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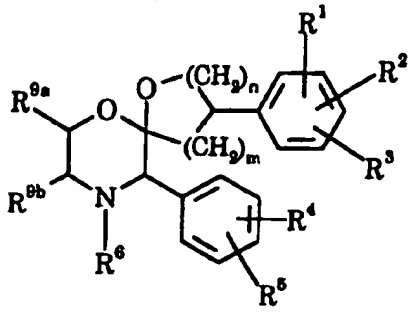
(54) Title: SPIROKETAL DERIVATIVES, COMPOSITIONS CONTAINING THEM AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

The present invention relates to spiroketal derivatives of formula (I) and pharmaceutically acceptable salts thereof wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b}, m and n are as defined in the specification, and to processes for their preparation, to intermediates used in their synthesis, to pharmaceutical compositions containing them, and to their use in therapy. The compounds are of particular use in the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia.



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SPIROKETAL DERIVATIVES, COMPOSITIONS CONTAINING THEM AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of spiroketal compounds which are useful as tachykinin antagonists. The present invention also relates to processes for their preparation, pharmaceutical compositions containing them, and to their use in therapy.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-NH_2

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the NK_1, NK_2 and NK_3 receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R.

Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in *1982 Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem*, (1982) 25, 1009) and in arthritis [Levine *et al Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al Neuroscience* (1988) 25(3), 817-37 and D. Regoli in *"Trends in Cluster Headache"* Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al, Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al, Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al, Science* (1988) 241, 1218-21 and Kimball *et al, J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al, PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing ß-amyloid-mediated neurodegenerative

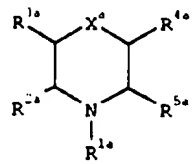
changes [Yankner *et al, Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al, Cancer Research* (1992) 52, 4554-7].

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

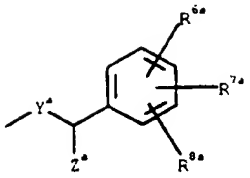
It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



wherein R^{1a} is a large variety of substituents;
R^{2a} and R^{3a} are *inter alia* hydrogen;

R^{4a} is *inter alia*



;

R^{5a} is *inter alia* optionally substituted phenyl;

R^{6a}, R^{7a} and R^{8a} are a variety of substituents;

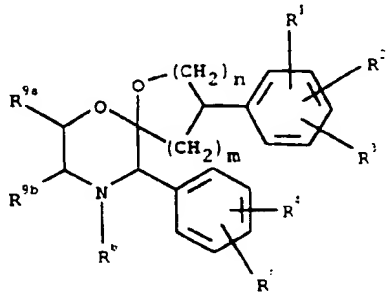
X^a is O, S, SO or SO_2;

Y^a is *inter alia* O; and

Z^a is hydrogen or C_{1-4}alkyl.

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

The present invention provides compounds of the formula (I):



(I)

wherein

R^1 represents hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, C_{1-4}alkyl substituted by a C_{1-4}alkoxy or hydroxy group, hydroxy, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, NR^aR^b, $SO_2NR^aR^b$, or OC_{1-4}alkylNR^aR^b, where R^a and R^b are each independently hydrogen or C_{1-4}alkyl;

R^2 and R^3 each independently represent hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or trifluoromethyl;

or, where R^1 and $R^2$are attached to adjacent carbon atoms, they may be joined such that, together with the carbon atoms to which they are attached, there is formed a 5- or 6-membered ring optionally containing 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen, or 1 or 2 groups selected from S(O), $S(O)_2$ and NR^a, which ring may also contain 1 or 2 double bonds, where R^a is as previously defined;

R^4 represents hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, C_{1-4}alkyl substituted by a C_{1-4}alkoxy group, trifluoromethyl, nitro, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$ where R^a and R^b are as previously defined;

R^5 represents hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or trifluoromethyl;

R^6 represents hydrogen, COR^a, CO_2R^a, $COCONR^aR^b$, $COCO_2R^a$, C_{1-6}alkyl optionally substituted by a group selected from (CO_2R^a, $CONR^aR^b$, hydroxy, CN, COR^a, NR^aR^b, $C(NOH)NR^aR^b$, CONHphenyl(C_{1-4}alkyl), $COCO_2R^a$, $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}$alkylR^{12}, $CONR^{13}C_{2-6}$alkenyl, $CONR^{13}C_{2-6}$alkynyl, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, $CONR^a$heteroaryl, and phenyl optionally substituted by one, two or three substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen and trifluoromethyl) or C_{1-6}alkyl, optionally substituted by oxo, substituted by a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkyl;

R^7 is hydrogen or C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen or C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkoxy optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} each independently represent hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

R^{12} represents OR^a, $CONR^aR^b$ or heteroaryl;

R^{13} represents H or C_{1-6}alkyl;

m is zero, 1, 2 or 3; and

n is zero, 1, 2 or 3; with the proviso that the sum total of m and n is 2 or 3;

and pharmaceutically acceptable salts thereof.

A preferred class of compound of formula (I) is that wherein R^1 represents hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, C_{1-4}alkyl substituted by a C_{1-4}alkoxy group, OCF_3, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$ where R^a and R^b are each independently hydrogen or C_{1-4}alkyl; and R^2 and R^3 each independently represent hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or trifluoromethyl.

Certain particularly apt compounds of the present invention include those wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halo or CF_3.

Most aptly R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Most aptly R^3 is hydrogen, fluorine, chlorine or CF_3.

Favourably R^1 is C_{1-4}alkoxy, especially methoxy, ethoxy, n-propoxy, i-propoxy or t-butoxy.

Favourably R^2 is hydrogen, fluorine, chlorine or C_{1-4}alkyl, especially hydrogen, fluorine, i-propyl, or t-butyl.

Favourably R^3 is hydrogen.

Preferably R^1 is in the 2-position on the phenyl ring.

Preferably R^2 is in the 5-position on the phenyl ring.

Most aptly R^4 is hydrogen.

Most aptly R^5 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

Most aptly R^{9a} and R^{9b} are each independently hydrogen or methyl.

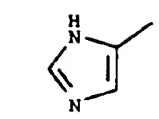
Preferably R^{9a} is hydrogen. Preferably R^{9b} is hydrogen. Most preferably R^{9a} and R^{9b} are both hydrogen.

Preferably n is 1.

Preferably m is 1 or 2, especially 1.

Favourably R^6 is C_{1-6}alkyl, in particular CH_2, $CH(CH_3)$ and CH_2CH_2 and especially CH_2, substituted by a 5-membered ring.

In particular, the 5-membered ring is a heterocyclic ring selected from: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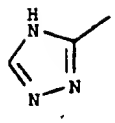
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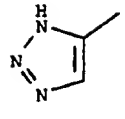
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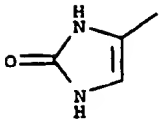
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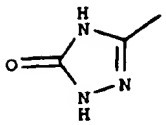
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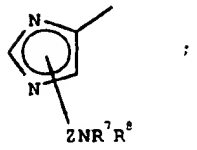
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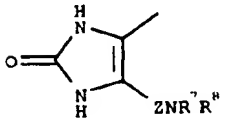
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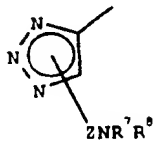
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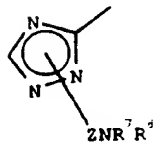
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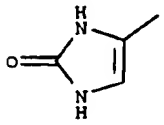
Particularly preferred heterocyclic rings are selected from: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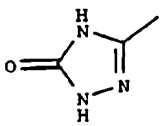
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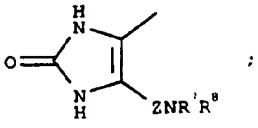
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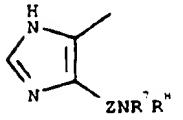
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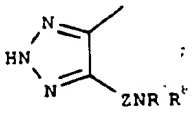
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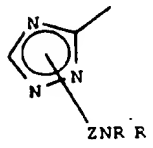
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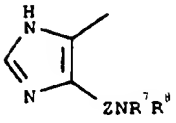
Most especially, the heterocyclic ring is selected from: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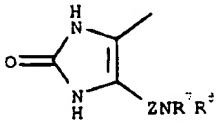
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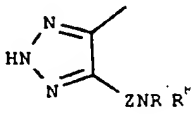
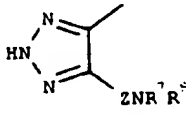
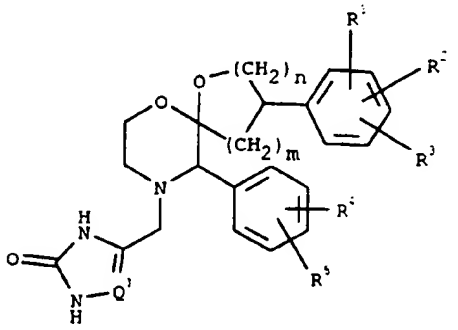

.

A particularly preferred heterocyclic ring is:


.

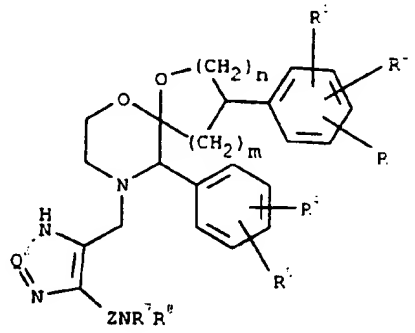
One favoured group of compounds of the present invention are of the formula (Ia) and pharmaceutically acceptable salts thereof:



(Ia)

wherein R^1, R^2, R^3, R^4, R^5, m and n are as defined in relation to formula (I) and Q^1 is CH, N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in relation to formula (I).

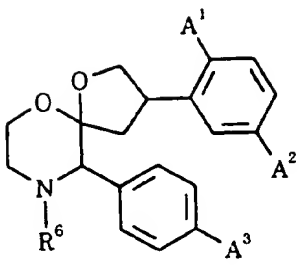
Another favoured group of compounds of the present invention are of the formula (Ib) and pharmaceutically acceptable salts thereof:



(Ib)

wherein R^1, R^2, R^3, R^4, R^5, m and n are defined in relation to formula (I), Q^2 is CH or N and Z, R^7 and R^8 are as defined in relation to formula (I).

A further favoured group of compounds of the present invention are of the formula (Ic) and pharmaceutically acceptable salts thereof:



(Ic)

wherein R^6 is as defined in relation to formula (I);

A^1 is C_{1-4}alkoxy;

A^2 is hydrogen, halogen, C_{1-4}alkyl or fluoroC_{1-4}alkyl; and

A^3 is hydrogen or halogen.

In particular, A^1 is preferably methoxy, ethoxy, n-propoxy or i-propoxy.

In particular A^2 is hydrogen, fluorine or trifluoromethyl.

In particular A^3 is hydrogen or fluorine.

With respect to compounds of the formulae (I), (Ia), (Ib) and (Ic), Z (where present), may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and most favourably 1 or 2 carbon atoms. A particularly favourable group Z is CH_2.

With respect to compounds of the formulae (I), (Ia), (Ib) and (Ic), R^7 may aptly be a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, R^8 may aptly be a C_{1-4}alkyl group or a C_{1-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, or R^7 and R^8 may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxy or C_{1-2}alkoxy group.

Where the group NR^7R^8 represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR^7R^8 represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R^8 represents a C_{2-4}alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR^7R^8 include those wherein Z is CH_2 or CH_2CH_2 and NR^7R^8 is amino, methylamino, dimethylamino, diethylamino, azetidinyl, pyrrolidino and morpholino.

Further preferred moieties represented by ZNR^7R^8 are those wherein Z is CH_2 or CH_2CH_2, R^7 represents hydrogen, C_{1-4}alkyl or C_{3-6}cycloalkyl and R^8 is C_{2-4}alkyl substituted by one or two substituents selected from hydroxy, C_{1-2}alkoxy, azetidinyl, pyrrolidino, piperidino, morpholino or thiomorpholino.

In particular, Z is preferably CH_2 and NR^7R^8 is preferably dimethylamino, azetidinyl or pyrrolidino, especially dimethylamino.

Where R^1 and R^2, together with the carbon atoms to which they are attached, form a 5- or 6-membered ring optionally containing 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen, or 1 or 2 groups selected from S(O), $S(O)_2$ and NR^a, and which ring may also contain 1 or 2 double bonds, it will be appreciated that the ring thus formed may be saturated, partially saturated or unsaturated. Thus, R^1 and R^2 may represent, for example, $-OCH_2CH_2CH_2-$, $-OCH_2CH_2O-$, $-OCH_2CH_2-$, $-OCH_2O-$, $-NR^aCH_2CH_2CH_2-$, $-NR^aCH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$,

$-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, -O-CH=CH-, $-NR^a-CH=CH-$, -S-CH=CH-, $-NR^a-CH=N-$, -O-CH=N-, -S-CH=N-, -N=CH-CH=CH-, -CH=N-CH=CH-. Particularly preferred linkages formed by R^1 and R^2 include , $-OCH_2CH_2CH_2-$, $-OCH_2CH_2O-$, $-OCH_2CH_2-$, $-OCH_2O-$, $-NR^aCH_2CH_2CH_2-$ and -CH=CH-CH=CH-. In these examples, R^a preferably represents a hydrogen atom.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

As used herein, the terms "fluoroC_{1-6}alkyl" and "fluoroC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by a fluorine atom. Particularly preferred are fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3 and OCF_3.

When used herein the term halogen means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred.

Specific compounds within the scope of this invention include:
(2S,3S,9R)-4-aza-1,7-dioxa-3,9-diphenylspiro[5.5]undecane;
(2S,3S,9S)-4-aza-1,7-dioxa-3,9-diphenyl-spiro[5,5]undecane;
(2R,3S,9S)-4-aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane;

(2R,3S,9R)-4-aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane;
(2S,3S,9S)-4-aza-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane-4-ylmethyl)-2,4-dihydro-1,2,4-triazol-3-one;
4-aza-4-benzyl-1,7-dioxa-3,8-diphenyl-spiro[5.4]decane;
and pharmaceutically acceptable salts thereof.

Further specific compounds within the scope of the present invention include:
(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-phenylspiro[5.4]decane;
(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl) spiro[5.4]decane;
(2R,3S,8R)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
(2R,3S,8S)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
(2R,3S,8R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
(2R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
(2R,3S,8R)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
(2R,3S,8S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;
4-aza-4-benzyl-7-dioxa-5-phenyl-9-(2-trifluoromethyl-phenyl)-spiro[5.5]undecane;
(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethylphenyl) spiro[5.5]undecane;
(3R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethylphenyl) spiro[5.5]undecane;
(2R,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl) phenyl)spiro[5.5]undecane;
(2S,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl)phenyl) spiro[5.5]undecane;

4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl) spiro[5.5]undecane;

(2R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2R,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-benzyl-7-dioxa-5-phenyl-9-(2-(trifluoromethoxy) phenyl)-spiro[5.5]undecane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy) phenyl)spiro[5.5]undecane;

4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)-spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-thiomethylphenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-1,7-dioxa-9-(5-fluoro-2-methoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-1,7-dioxa-9-(5-fluoro-2-isopropoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-benzyl-9-(2,5-dimethoxyphenyl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-(carbonylmethylpyrrolidin-1-yl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane;

and pharmaceutically acceptable salts thereof.

Yet further specific compounds within the scope of the present invention include those compounds listed in Tables 1 and 2 and pharmaceutically acceptable salts thereof.

In a further aspect of the present invention, the compounds of formula (I) will preferably be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as

alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

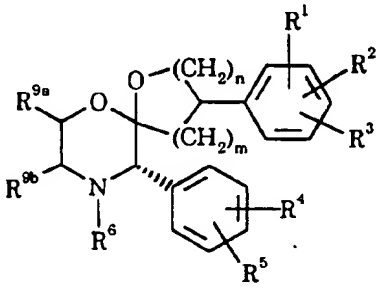
The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I), (Ia), (Ib) and (Ic) will have the preferred stereochemistry of the 3-position that is possessed by the compound of Example 1 (i.e. 3-(S)). Thus for example as shown in formula (Id)



(Id)

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of

the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0μm, particularly 0.1 and 0.5μm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I),

which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine,

hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those

associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neurogangliobiastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as

rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly

used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT_3 antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-

R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D_4 antagonist such

as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT_1 agonists, especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac,

ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

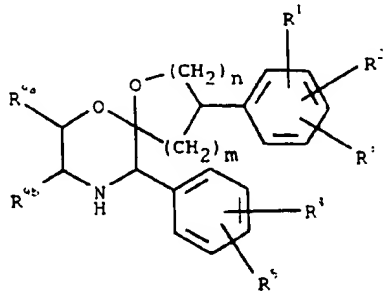
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from a compound of formula (I) in which R^6 is H, hereinafter referred to as compounds of formula (II)



(II)

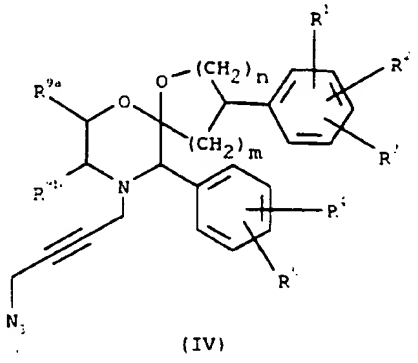
wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, m and n are as defined in relation to formula (I) by reaction with a compound of formula (III):

$$LG\text{-}R^{6a} \qquad (III)$$

where R^{6a} is a group of the formula R^6 as defined in relation to formula (I) or a precursor therefor and LG is a leaving group such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or a halogen atom (e.g. bromine, chlorine or iodine); and, if R^{6a} is a precursor group, converting it to a group R^6 (in which process any reactive group may be protected and thereafter deprotected if desired).

This reaction may be performed in conventional manner, for example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

According to another process (B), compounds of formula (I) wherein R^6 represents a 1,2,3-triazol-4-ylmethyl group substituted by $CH_2NR^7R^8$, may be prepared by reaction of a compound of formula (IV)

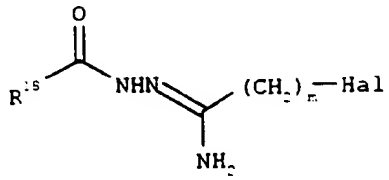


(IV)

with an amine of formula NHR^7R^8, in a suitable solvent such as an ether, for example, dioxan, at elevated temperature, for example, between 50°C and 100°C, in a sealed tube, or the like. This reaction is based upon that described in *Chemische Berichte* (1989) 122, p. 1963.

According to a further process (C), compounds of formula (I) wherein R^6 represents a C_{1-6}alkyl group which is substituted by an

unsubstituted or substituted 1,2,4-triazolyl group, may be prepared by reaction of an intermediate of formula (II) with a compound of formula (V)



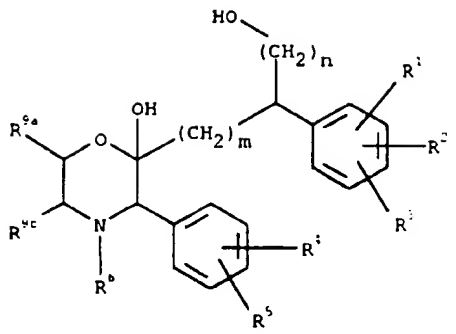
(V)

wherein Hal is a halogen atom, for example, bromine, chlorine or iodine, m is an integer from 1 to 6 and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I), for example, by reduction of the $CONH_2$ group to CH_2NH_2.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as about 140°C.

A suitable reducing agent for the group $CONH_2$ is lithium aluminium hydride, used at between -10°C and room temperature.

According to another process, (D), compounds of formula (I) may be prepared from intermediates of formula (VI)



(VI)

by an acid catalysed intramolecular cyclisation reaction.

Suitable acids of use in the reaction include mineral acids such as, for example, hydrochloric acid. The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. methanol, at elevated temperature, for example, at the reflux temperature of the chosen solvent.

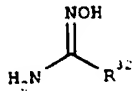
Further details of suitable procedures will be found in the accompanying Examples.

According to a further process (E), compounds of formula (I) may also be prepared from other compounds of formula (I) using suitable interconversion procedures. In particular, interconversion processes may be used to vary the group R^6. For example, compounds of formula (I) wherein R^6 is other than H may be prepared from the corresponding compounds of formula (I) wherein R^6 is H by reaction with a reagent suitable to introduce the group R^6, for example, compounds of formula (I) wherein R^6 is COR^a may be prepared from compounds of formula (I) wherein R^6 is H by, for example, reaction with an appropriate acid anhydride.

Compounds of formula (I) wherein R^6 is C_{1-6}alkyl may be prepared from corresponding compounds of formula (I) wherein R^6 is COR^a by reduction using, for example, borane or a borohydride such as sodium cyanoborohydride.

Compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by $CONR^aR^b$ may be prepared from corresponding compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by CO_2R^a by treatment with ammonia or an amine of formula NR^aR^b.

Compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by 5-oxadiazolyl may be prepared from compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by CO_2R^a, where R^a represents C_{1-6}alkyl, by reaction with a compound of formula (VII)



(VII)

wherein R^{32} represents H or a suitable substituent, in the presence of a base.

Suitable bases of use in the reaction include alkali metals, such as, for example, sodium, and alkali metal hydrides, such as, for example, sodium hydride.

The reaction is conveniently effected in a suitable organic solvent. Which solvents will be appropriate will depend on the nature of the base used. For example, where the base used is an alkali metal, suitable solvents will include alcohols, for example, ethanol, whereas where the base used is an alkali hydride, suitable solvents will include ethers, for example, tetrahydrofuran.

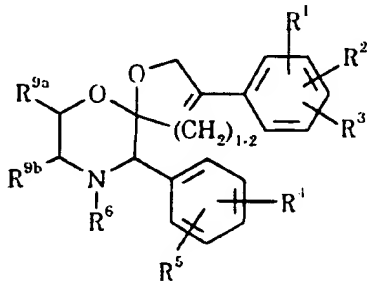
Preferably the reaction is conducted at elevated temperature, such as the reflux temperature of the chosen solvent.

Compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by thiazolyl may be prepared from compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by $CSNH_2$ by reaction with a compound of formula $Hal\text{-}CH_2C(O)\text{-}R^{60}$, where Hal is a halogen atom, such as bromine, chlorine or iodine, and R^{60} represents H or a suitable substituent.

Compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by thioxotriazolyl may be prepared from compounds of formula (I) wherein R^6 is C_{1-6}alkyl substituted by $CONHNH_2$ by reaction with a compound of formula $R^{61}NCS$, wherein R^{61} represents H or a suitable substituent such as C_{1-6}alkyl, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

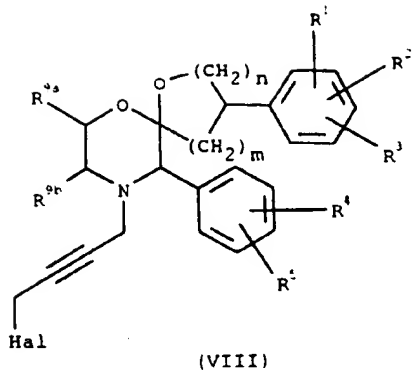
According to a further general process (F) compounds of formula (I) in which n is 1 and m is 1 or 2, may be prepared by the reduction of a compound of formula (XX)



(XX)

Suitable reducing conditions include: catalytic hydrogenation using a metal catalyst such as palladium or platinum or hydroxides or oxides thereof, preferably in a suitable solvent such as alcohol, e.g. methanol or ethanol, or an ester, e.g. ethyl acetate, or an organic acid e.g. acetic acid, or a mixture thereof; borane in tetrahydrofuran; 9-boracyclo[3.3.1]nonane (9-BBN) in an ether such as tetrahydrofuran; and lithium triethylborohydride (Super-Hydride™) in an ether such as tetrahydrofuran.

Intermediates of formula (IV) may be prepared from a compound of formula (VIII)



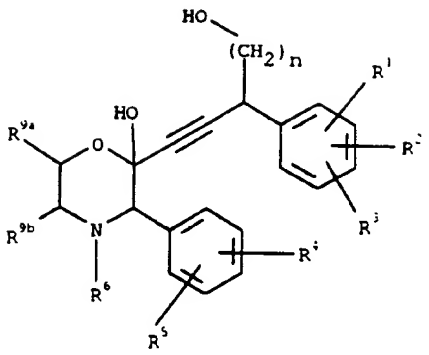
(VIII)

wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially chlorine, by reaction with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at or below room temperature.

Compounds of formula (VIII) may be prepared by a dropwise addition of an intermediate of formula (II) to a dihaloacetylene of formula Hal-CH_2-C≡C-CH_2-Hal where each Hal is independently chlorine, bromine or iodine, especially chlorine. The reaction is conveniently effected in a suitable solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Compounds of formula (V) may be prepared as described in *J. Med. Chem.*, (1984) 27, 849.

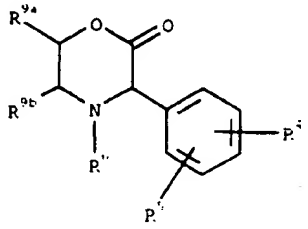
Intermediates of formula (VI) wherein m is 2 may be prepared by the reduction of a compound of formula (IX):



(IX)

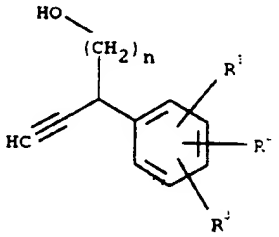
or a protected derivative thereof, using conventional methodology, for instance, by catalytic hydrogenation using a metal catalyst such as palladium or platinum or oxides thereof, preferably in a solvent such as an alcohol, e.g. ethanol, or an ester, e.g. ethyl acetate.

Compounds of formula (IX) may be prepared by the reaction of a compound of formula (X):



(X)

with a compound of formula (XI):



(XI)

or a protected derivative thereof, by lithiation using n-butyl lithium followed by quenching with, for example, sodium dihydrogen orthophosphate. The reaction is conveniently effected in a solvent such

as an ether, e.g. tetrahydrofuran, at reduced temperature, for example, at -78°C.

Compounds of formula (X) may be prepared by methods descibed in European Patent Specification No. 0 577 394-A, or by analogous methods.

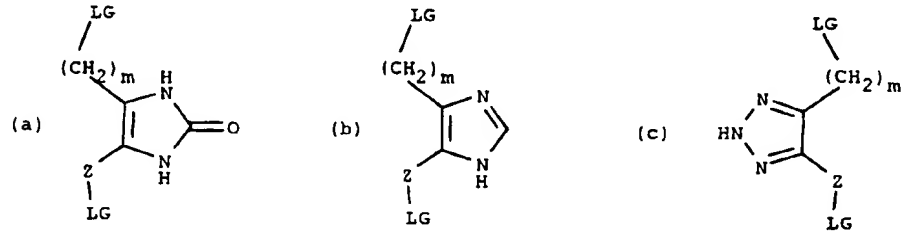
Compounds of formula (XI) are known compounds (see *Chemische Berichte*, (1988) 121, 1315-1320) or may be prepared by analogous methods.

For compounds wherein R^6 is a C_{1-6}alkyl group substituted by a 5-membered heterocycle which in turn is substituted by a ZNR^7R^8 group where Z is CH_2, certain favoured compounds of formula (I) may be prepared from a corresponding compound with a hydrogen atom in place of the ZNR^7R^8. Thus, for example a compound of the formula (I) wherein R^6 is an imidazolinone group carrying a $CH_2NR^7R^8$ moiety may be prepared from a corresponding compound lacking the $CH_2NR^7R^8$ moiety by reaction with formaldehyde and an amine NHR^7R^8 under conventional Mannich reaction conditions, for example in methanol with heating. If desired a pre-formed reagent such as $R^7R^8N^+=CH_2.I^-$ may be employed and a tertiary amine such as triethylamine used as acid acceptor.

Alternatively a compound of formula (I) wherein R^6 is a C_{1-6}alkyl group substituted by an imidazolinone group may be reacted with paraformaldehyde and an amine for example a secondary amine such as pyrrolidine or morpholine to give a compound wherein the imidazolinone ring is substituted by $CH_2NR^7R^8$ where R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety, where R^c is as previously defined.

This reaction may be performed in a conventional manner, for instance. in a suitable solvent such as an alcohol, for example, methanol at an elevated temperature up to the boiling point of the solvent.

A further alternative method for the preparation of certain compounds of formula (I) involves the reaction of an intermediate of formula (II) as defined above with one of the compounds of formula (XII):



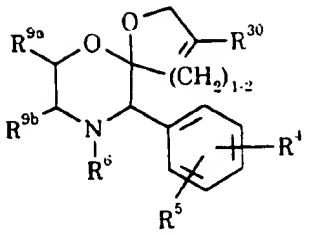
(XII)

wherein each LG, which may be the same or different, is a leaving group, such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or, in particular, a halogen atom, (e.g. bromine, chlorine or iodine), m is an integer from 1 to 6 and X and Z are as defined in formula (I), followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety.

This reaction is conveniently effected in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

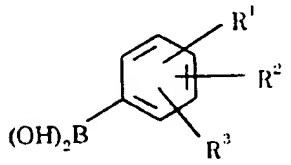
It will be appreciated that, where necessary, reactive groups may be protected, thus for example, the NH groups of an imidazolinone of formula (XIIa) may be protected by any suitable amine protecting group such as an acetyl group.

Compounds of formula (XX) may be prepared by the reaction of a compound of formula (XXI):



(XXI)

wherein R^{30} is a suitable leaving group such as $-OSO_2CF_3$, with a boronic acid of formula (XXII):

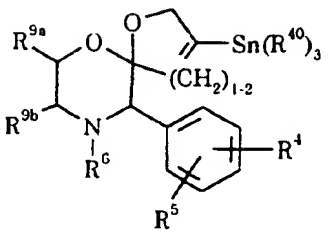


(XXII)

or an ester or an anhydride thereof.

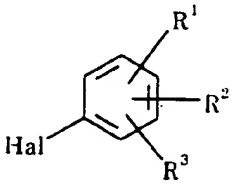
The reaction is preferably effected in the presence of a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (0) in a suitable solvent such as an ether, for example, tetrahydrofuran or 1,2-dimethoxyethane, in the presence or absence of water, or an aromatic hydrocarbon, for example, benzene. The reaction is preferably effected in the presence of a base such as an alkali or alkaline earth metal carbonate, for example, sodium carbonate, at a suitable temperature up to reflux.

Alternatively, compounds of formula (XX) may be prepared by the reaction of a compound of formula (XXIV)



(XXIV)

wherein each R^{40} is a C_{1-4}alkyl group, preferably methyl groups, with a compound of formula (XXV)



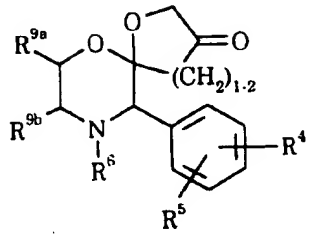
(XXV)

wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially bromine.

The reaction is conveniently effected in the presence of lithium chloride and a transition metal catalyst such as triphenylphosphine palladium(0). Suitable solvents for the reaction include aromatic hydrocarbons, for example, toluene, the reaction being effected at a temperature between 80°C and the reflux temperature of the solvent.

Compounds of formula (XXIV) may be prepared from a corresponding compound of formula (XXI) by reaction with a compound of the formula $(R^{40})_3Sn\text{-}Sn(R^{40})_3$, for example, hexamethyl distannane. The reaction is conveniently effected in the presence of a base, for example, lithium carbonate, and a catalyst such as triphenylphosphine palladium(0). Suitable solvents for the reaction include ethers, such as tetrahydrofuran, the reaction being effected at a temperature between room temperature and 100°C, for example, at about 60°C.

Compounds of formula (XXI) may be prepared from a compound of formula (XXIII):



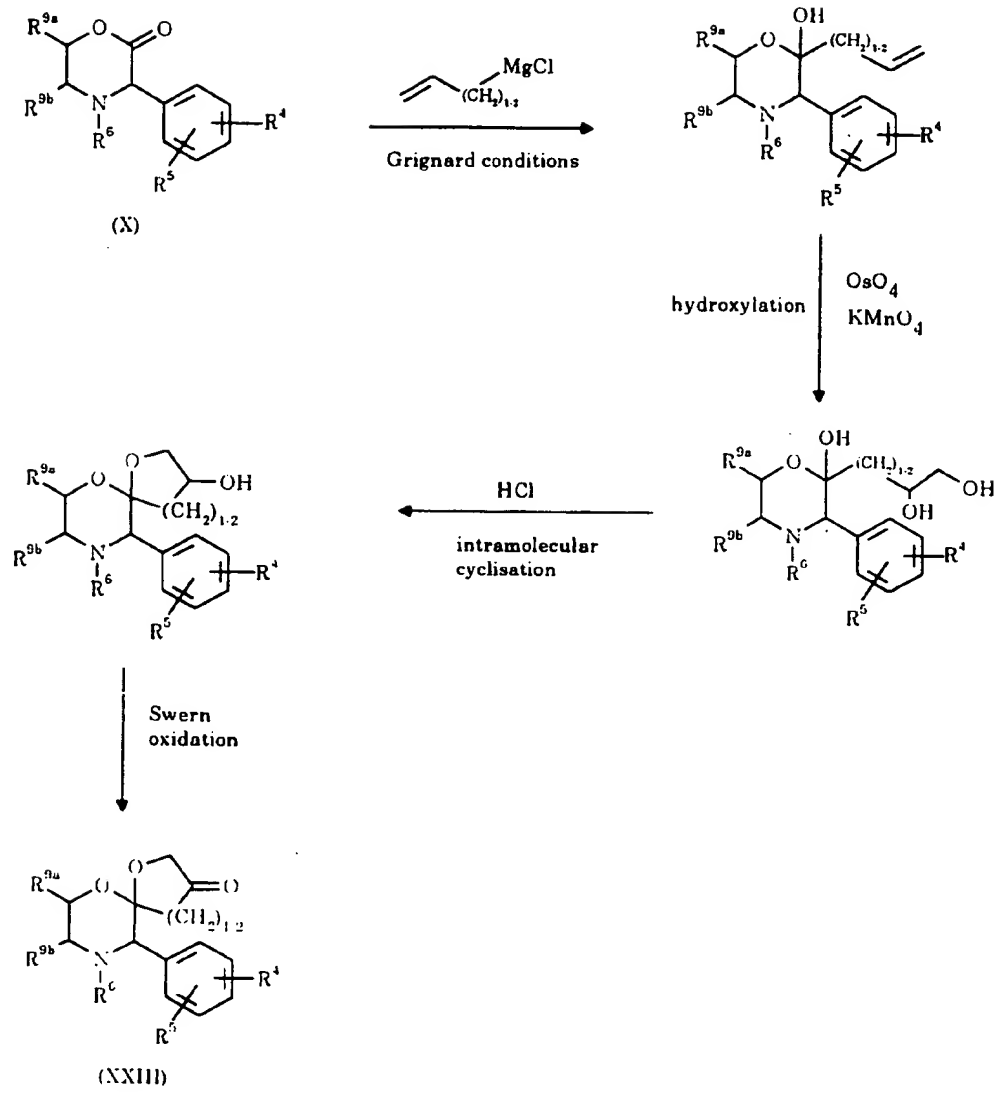
(XXIII)

by enolisation of the ketone in the presence of a base, for example, sodium hexamethyldisilazide, followed by reaction with a reagent capable of introducing a suitable leaving group, for instance, where R^{30} is $-OSO_2CF_3$, using 2-[N,N-bis(trifluoromethylsulphonyl)amino]-5-chloropyridine or triflic anhydride. The reaction is conveniently effected in a suitable solvent such as an ether, for example, tetrahydrofuran at a reduced temperature, for instance, -78°C.

Compounds of formula (XXII) and (XXV) are either known compounds or may be prepared in a conventional manner using standard methodology or methods analogous to those described herein.

Compounds of formula (XXIII) may be prepared from a compound of formula (X) by the reaction sequence of Scheme 1 or by methods analogous thereto:

Scheme 1



(X)

(XXIII)

In a preferred embodiment of the aforementioned processes, R^6 is a benzyl group. The reduction reaction described as process (G) above for the preparation of compounds of formula (XX) may conveniently replace the benzyl group with a hydrogen atom. It will be appreciated from the discussion above that compounds of formula (I) wherein R^6 is a hydrogen atom are particularly preferred precursors to other compounds of formula (I).

It will be appreciated that compounds of the formula (I) wherein R^6 contains an =O or =S substituent can exist in tautomeric forms. All such tautomeric forms and mixtures thereof are included within this invention. Most aptly the =O or =S substituent in R^6 is the =O substituent.

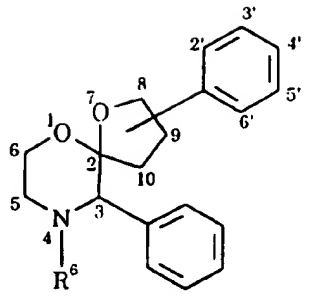
Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

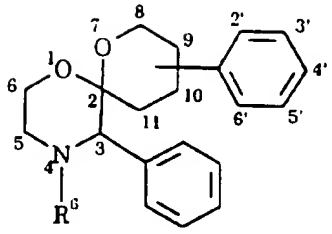
Further methods suitable for adaptation to the preparation of the spiroketal compounds of the present invention are described by F. Perron and K.F. Albizati in *Chem. Rev.*, (1989) 89, 1617-1661.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds or, in the case of prodrugs, the parent compounds, were found to be active with IC_{50} at the NK_1 receptor of less than 1μM on said test method.

For the avoidance of doubt, the nomenclature adhered to throughout this specification is based upon the following structures:



and



The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

DESCRIPTION 1

2-Phenyl-but-3-yn-1-ol

2-Phenyl-4-trimethylsilyl-but-3-yn-1-ol (*Chem. Ber.* (1988), 121, 1315-1320) (7.8g) was dissolved in ethanol and the solution was cooled to -5°C. A solution of silver nitrate (8.9g) in ethanol (60ml) and water (21ml) was added dropwise to the acetylene solution such that the temperature remained below 5°C. This precipitated the acetylene as the silver complex. A solution of potassium cyanide (17g) in water (30ml) was added dropwise to the stirred acetylene mixture and the resulting mixture was stirred at room temperature for 30 minutes. The mixture mainly dissolved and was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified on silica using 10% ethyl acetate in hexane as eluant to afford the title compound (5g) as a colourless oil.

^1H NMR (360MHz, $CDCl_3$) δ 2.35 (1H, d, J=3Hz), 3.75-3.83 (2H, m), 3.83-3.91 (1H, m), 7.25-7.43 (5H, m).

DESCRIPTION 2

tert-Butyldimethylsilyloxy-2-phenyl-but-3-yne

The product of Description 1 (5g) was dissolved in dichloromethane at 0°C under nitrogen. 2,6-Lutidine (4.8ml) was added to the solution

followed by dropwise addition of *tert*-butyldimethylsilyl trifluoromethane sulfonate (9.44ml); the resulting solution was stirred overnight at room temperature. The solution was washed with water (x3), brine and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified on silica using 1-5% diethyl ether in hexane as eluant to afford the title compound as a pale yellow oil (8.8g). ^1H NMR (360MHz, $CDCl_3$) δ 0.36 (6H, s), 0.91 (9H, s), 2.33 (1H, d, J=3Hz), 3.77-3.81 (1H, dd), 3.82-3.88 (1H, m), 3.91-3.97 (1H, dd), 7.29-7.47 (5H, m).

DESCRIPTION 3

4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-but-1-ynyl]-3-phenyl-morpholin-2-ol

The product of Description 2 (8.8g) was dissolved in tetrahydrofuran (100ml, anhydrous) and the solution was cooled to -78°C. n-Butyl lithium (28.8ml, 1.6M in hexane) was added dropwise such that the internal temperature was maintained below -70°C. The resulting solution was stirred for 1h. 4-Benzyl-3-(S)-phenyl-2-morpholinone (see European Patent Specification No. 0577394-A) (10.1g) was dissolved in tetrahydrofuran (50ml) and was cooled to -78°C. This solution was added dropwise to the acetylide solution and the resulting reaction mixture was stirred at -78°C for 1h. The mixture was allowed to warm to 0°C and was quenched with sodium dihydrogen phosphate (250ml, 10% aqueous solution). Tetrahydrofuran was removed *in vacuo* and the residue was extracted into ethyl acetate (x3). The combined organic solution was washed with water and brine, then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified on silica using 5-15% ethyl acetate in hexane as eluant to afford the product as a mixture of inseparable isomers (7.5g). The yellow oil was not purified further but was taken on to the next step. MS CI^+ m/z 528 ($M+1^+$, 100%).

DESCRIPTION 4

4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-butyl]-3-phenyl-morpholin-2-ol

The compound described in Description 3 was dissolved in ethyl acetate and a suspension of platinum oxide (500mg) in ethyl acetate was added. The mixture was hydrogenated at 40psi for 2h. The catalyst was removed by filtration and the solvent was removed *in vacuo* to afford the product as a mixture of isomers. This mixture (7.3g) was used in the next step without purification. MS CI^+ m/z 532 ($M+1^+$, 100%).

DESCRIPTION 5

4-Benzyl-2-(4-hydroxy-3-phenyl-butyl)-3-phenyl-morpholin-2-ol

The silyl ether described in Description 4 (7.3g) was dissolved in methanol. Methanolic hydrogen chloride (14ml, 1M) was added followed by Amberlyst catalyst (300mg). An additional aliquot of methanolic hydrogen chloride was added to the mixture and the reaction mixture was stirred for 2h. The mixture was filtered and concentrated to yield a yellow oil (5g). This diol was used in the next reaction without purification. MS CI^+ m/z 418 ($M+1^+$, 90%).

DESCRIPTION 6

tert-Butyldimethylsilyloxy-1-phenyl-prop-1-yne

1-Phenyl-2-propyn-1-ol (7g) was dissolved in dichloromethane at 0°C under nitrogen. 2,6-Lutidine (6.17ml) was added to the solution followed by dropwise addition of *tert*-butyldimethylsilyl trifluoromethane sulfonate (12.16ml); the resulting solution was stirred overnight at room temperature. The dichloromethane was washed with water (2x), brine and dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was purified on flash silica using 100% petrol moving to 5% ethyl acetate/petrol, to afford the title compound as a yellow oil (10.31g).

^{1}H NMR (250MHz, $CDCl_3$) δ 0.18 (3H, s), 0.2 (3H, s), 0.96 (9H, s), 2.55 (1H, d, J=2Hz), 5.49 (1H, d, J=2Hz), 7.26-7.40 (3H, m), 7.48-7.53 (2H, m).

DESCRIPTION 7

4-Benzyl-2-[3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-prop-1-ynyl]-3-phenyl-morpholin-2-ol

The product of Description 6 (5g) was dissolved in dry THF (40ml) and cooled to -78°C. n-Butyl lithium (1.6M in hexane; 13.9ml) was added dropwise and stirred for 1 hour; the colour changed to an orange/red colour. 3-(S)-Phenyl-4-benzyl-2-morpholinone (5.4g) was dissolved in tetrahydrofuran, cooled to -78°C and added dropwise to the acetylide. The reaction was stirred overnight. The reaction was quenched with sodium dihydrogen orthophosphate and extracted with ethyl acetate (3x100ml). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated to afford a brown oil. Purification was carried out on flash silica eluted with 5-15% ethyl acetate in hexane which afforded the title compound. MS CI^+ m/z 514 ($M+1^+$, 100%).

DESCRIPTION 8

4-Benzyl-2-[3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-propyl]-3-phenyl-morpholin-2-ol

The silyl ether described in Description 7 (1g) was dissolved in ethyl acetate (50ml) and wetted platinium (IV) oxide (200mg) was added. The reaction was placed under an atmosphere of hydrogen (30psi) for 1 hour. The catalyst was removed by filtration and the solvent removed *in vacuo* to afford the title compound. MS CI^+ m/z 518 ($M+1^+$, 100%).

DESCRIPTION 9

4-Benzyl-2-(3-hydroxy-3-phenyl-propyl)-3-phenyl-morpholin-2-ol

The saturated silyl ether described in Description 8 (1g) was dissolved in dry methanol (10ml), methanol hydrogen chloride (5ml) and

Amberlyst catalyst were added and the reaction was stirred for one hour. The catalyst was removed by filtration and the solvent was removed *in vacuo* to afford a yellow oil. The oil was dispersed between ethyl acetate and sodium carbonate solution. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a yellow oil. Purification was carried out on flash silica eluted with 20-30% ethyl acetate in petrol to give the title compound (0.32g). MS CI^+ m/z 404 ($M+1^+$, 100%).

DESCRIPTION 10

(2R,3S)-4-Benzyl-3-(4-fluorophenyl)-2-hydroxy-2-(prop-2-enyl)morpholine

(3S)-4-Benzyl-3-(4-fluorophenyl)-2-morpholinone (13.6g, 47.6mmol) was dissolved in anhydrous tetrahydrofuran (200ml) and cooled to below -70°C under an inert atmosphere. Allyl magnesium chloride (26.2ml of a 2.0M solution in tetrahydrofuran; 52.4mmol) was added dropwise over 15 minutes, maintaining the temperature below -70°C. After 30 minutes, the reaction was quenched by the addition of a saturated solution of ammonium chloride and allowed to warm to room temperature. The resulting suspension was extracted with ethyl acetate (3x100ml), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound in ~3:1 mixture of the lactols as a light yellow oil (15.3g, 98%), which was used without further purification. MS (ES^+) m/z 328 (M+1, 22%), 310 (M-OH, 61), 269 (100).

DESCRIPTION 11

(2R,3S)-4-Benzyl-2-(2,3-dihydroxy)propyl-3-(4-fluorophenyl)-2-hydroxymorpholine

The alkene of Description 10 (18.9g, 57.7mmol) was stirred with osmium tetroxide (0.2g, 0.8mmol) and N-methylmorpholine N-oxide (7.78g, 66.4mmol) in a solution of tetrahydrofuran (200ml), 2-methyl-2-propanol (120ml) and water (14ml) for 3 days at room temperature. The

resulting black solution was diluted with ethyl acetate (200ml), water (200ml) and saturated brine (100ml), separated and the organic fraction dried ($MgSO_4$) and concentrated *in vacuo*. The resulting black oil (26g) was purified by flash silica gel chromatography eluting with 50-100% ethyl acetate in hexane to yield the title compound as a mixture of isomers as a white foam (15.9g, 76%).

Analysis: $C_{20}H_{24}FNO_4$. 0.5 H_2O requires C, 64.84; H, 6.82; N, 3.78;
Found: C, 65.22; H, 6.74; N, 3.68%

MS (ES^+) 362 (M+1, 18%), 344 (M-OH, 100).

DESCRIPTION 12

(2R,3S,9RS)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-hydroxyspiro[5,4]decane and (2S,3S,9RS)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-hydroxyspiro[5,4]decane

The mixture of triols of Description 11 (15.0g, 41.5mmol) was dissolved in hydrochloric acid (200ml, 6M), and methanol (100ml) and heated at reflux for 5 hours. The cooled solution was basified with 4N sodium hydroxide solution and extracted with ethyl acetate (3x200ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting black oil (18g) was purified by flash silica gel chromatography eluting with 33-66% ethyl acetate in hexane to yield the title compounds as pairs of diasteromers.

Isomer pair A, less polar, an orange gum (7.1g, 50%). R_f 0.37 (50% ethyl acetate/hexane). ^1H NMR (360MHz, $CDCl_3$) δ 0.42 (~½H, d, J=10.4Hz)*, 1.69 (½H, dd, J=13.5, 5.5Hz), 1.86 (½H, d, J=14.6Hz), 1.96 (½H, d, J=13.6Hz), 2.15 (½H, dd, J=14.6, 6.4Hz), 2.30 (1H, dt, J=12.0, 3.6Hz), 2.76 (1H, d, J=13.1Hz), 2.79 (1H, d, J=13.2Hz), 3.11 (~½H, d, J=11.2Hz)*, 3.34 (1H, d, J=14.2Hz), 3.35-3.71 (3H, m), 3.91 (½H, dd, J=9.7, 3.6Hz), 3.98-4.24 (2½H, m), 7.01 (2x½H, t, J=8.8Hz), 7.08 (2x½H, t, J=8.7Hz), 7.18-7.29 (5H, m), 7.54 and 7.63 (2H, 2xbr s) (* exchanges in D_2O); MS (ES^+) 344 (M+1, 100%).

Isomer B, more polar, an orange glass (4.3g, 30%). R_f 0.25 (50% ethyl acetate/hexane). ^1H NMR (360MHz, $CDCl_3$) δ 0.83 ($^2/_3H$, br d)*, 1.64 ($^1/_3H$, dd, J=14.0, 5.7Hz), 1.87 ($^2/_3H$, d, J=14.6Hz), 2.02 ($^1/_3H$, J=14.0Hz), 2.15 ($^2/_3H$, dd, J=14.6, 6.6Hz), 2.32-2.41 (1H, m), 2.74-2.82 (1H, m), 3.03 ($^1/_3H$, d, J=11.0Hz)*, 3.14 ($^2/_3H$, d, J=13.7Hz), 3.17 ($^1/_3H$, d, J=13.7Hz), 3.50 ($^1/_3H$, d, J=13.6Hz), 3.59 ($^2/_3H$, d, J=13.7Hz), 3.66-4.16 ($5^1/_3H$, m), 4.33 ($^2/_3H$, br s), 7.00-7.09 (2H total, m), 7.21-7.31 (5H, m), 7.41-7.52 (2H total, m) (* exchanges in D_2O); MS (ES^+) 344 (M+1, 100%).

DESCRIPTION 13

(2R,3S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-oxospiro[5.4]decane

Anhydrous dimethylsulphoxide (3.4ml, 47.8mmol) dissolved in dichloromethane (10ml) was added dropwise over 10 minutes to a solution of oxalyl chloride (2.0ml, 22.9mmol) dissolved in anhydrous dichloromethane (200ml) cooled to below -70°C. The temperature was maintained below -60°C during the addition and the solution stirred for a further 15 minutes at below -70°C. The alcohol isomer pair A of Description 12 (6.57g, 19.1mmol) dissolved in dichloromethane (40ml) was added dropwise over 10 minutes, maintaining the temperature below -70°C, and then stirred at this temperature for one hour. Triethylamine (13.3ml, 95.5mmol) was added dropwise over 10 minutes, and the reaction allowed to warm to room temperature. The resulting mixture was washed with dilute sodium bicarbonate solution (0.2M) and water (200ml) and the organic fraction dried ($MgSO_4$) and concentrated *in vacuo* (7.9g). The crude product was purified by flash silica gel chromatography eluting with 14-20% ethyl acetate in hexane to yield the title compound as a pale yellow glass which solidified to a buff coloured solid on standing (5.2g, 80%).

Analysis: $C_{20}H_{20}FNO_3$ requires C, 70.37; H. 5.91; N, 4.10;
Found: C, 70.29; H, 5.83; N, 4.02%

$[\alpha]^{22}_D$=+125.6 (c=1.04, CH_2Cl_2); ^1H NMR (360MHz, $CDCl_3$) δ 2.31 (2H, d,

J=3.0Hz), 2.35 (1H, dt, J=12.0, 3.5Hz), 2.80 (1H, d, J=12.9Hz), 2.83 (1H, br d, J=11.0Hz), 3.52 (1H, s), 3.59 (1H, dq, J=10.1, 1.6Hz), 3.68 (1H, d, J=13.2Hz), 3.88 (1H, d, J=16.6Hz), 4.03 (1H, d, J=16.6Hz), 4.18 (1H, dt, J=11.7, 2.5Hz), 7.05 (1H, t, J=8.7Hz), 7.19-7.32 (5H, m), 7.58 (2H, br s); MS (ES^+) 342 (M+1, 100%).

DESCRIPTION 14

(2R,3S)-(4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]dec-9-en-9-yl) trifluoromethanesulfonate

The ketone of Description 13 (4.0g, 11.7mmol) as a solution in anhydrous tetrahydrofuran (16ml) was added dropwise over 10 mintes to a solution of sodium bis(trimethylsilyl)amide (14.0ml of 1.0M solution in tetrahydrofuran; 14.0mmol) cooled to below -70°C. The reaction mixture was stirred at this temperature for 2 hours before the addition of 2-[*N*,*N*-bis(trifluoromethylsulphonyl)amino]-5-chloropyridine (6.44g, 16.4mmol) in several portions. The solution was stirred at below -70°C for ½ hour before being allowed to warm to room temperature overnight. The reaction was quenched with a saturated ammonium chloride solution (60ml) and extracted with ethyl acetate (3x30ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude oil (13.2g) which was further purified by flash silica gel chromatography eluting with 10% ethyl acetate in hexane to yield the title compound as an orange oil (3.21g, 58%) and recovered ketone (0.51g, 13%). ^1H NMR (360MHz, $CDCl_3$) δ 2.33 (1H, dt, J=12.0, 3.5Hz), 2.83 (2H, d, J=13.5Hz), 3.50 (1H, s), 3.68 (1H, m), 3.73 (1H, d, J=13.4Hz), 3.94 (1H, dd, J=13.1, 2.1Hz), 4.25 (1H, dt, J=11.7, 2.5Hz), 4.57 (1H, dd, J=13.2, 2.1Hz), 5.60 (1H, t, J=2.0Hz), 7.01 (2H, t, J=8.7Hz), 7.22-7.31 (5H, m), 7.48 (2H, br s); MS (ES^+) 474 (M+1, 100%).

DESCRIPTION 15

(2-Methoxyphenyl)boronic acid

n-Butyl lithium (13.0ml of a 1.6M solution in hexanes, 19.8mmol) was added dropwise to a solution of 2-bromoanisole (3.74g, 19.0mmol) in anhydrous tetrahydrofuran (15ml) cooled to below -70°C, maintaining the temperature during the addition below -60°C. The solution was stirred for 20 minutes before the addition of trimethyl borate (5.9ml, 57.0mmol), and then stirred at below -70°C for a further hour before warming to room temperature overnight. The reaction mixture was cooled to 0°C acidified to pH 5.0 with 5% aqueous hydrochloric acid solution (25ml), the resulting layers separated and the aqueous phase extracted with ethyl acetate (2x25ml). The combined orgnic layers were washed with brine (25ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a white solid (2.9g, 97%) which was used without further purification.

DESCRIPTION 16

(2-(3RS)-RS,3S)-4-Benzyl-2-[3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-prop-1-ynyl]-3-(4-fluorophenyl)-morpholin-2-ol

The title compound was prepared from the product of Description 6 (19.7g, 79.9mmol) and (3S)-4-benzyl-3-(4-fluorophenyl)-2-morpholinone (22.8g, 80.0mmol) according to the method of Description 7 as an orange oil (29.5g, 69%). MS (ES^+) 532 (M+1, 100%), 514 (M-OH, 20).

DESCRIPTION 17

(2-(3RS)-RS,3S)-4-Benzyl-2-[3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-propyl]-3-(4-fluorophenyl)-morpholin-2-ol

The title compound was prepared from the product of Description 16 (22.0g, 41.3mmol) according to the method of Description 8 as a crude oil (15.6g, 70%). MS (ES^+) 536 (M+1, 100%), 518 (M-OH, 92).

DESCRIPTION 18

(2-(3RS)-RS,3S)-4-Benzyl-3-(4-fluorophenyl)-2-hydroxy-2-(3-hydroxy-3-phenyl-propyl)-morpholin-2-ol

The title compound was prepared from the product of Description 17 (15.6g, 29.1mmol) according to the method of Description 9 as a viscous oil (5.3g, 43%). MS (ES^+) 422 (M+1, 55%), 404 (M-OH, 100).

DESCRIPTION 19

2-(2-Trifluoromethyl-phenyl)oxirane

α,α,α-trifluoro-*o*-tolualdehyde (3g) was dissolved in anhydrous tetrahydrofuran and cooled to -78°C, iodochloromethane (1.38ml) was then added, followed by methyllithium (1.5M complexed with lithium bromide) (12ml) added over 5 minutes. The reaction was left to warm up to room temperature overnight. The reaction was quenched using saturated ammonium chloride solution and extracted using diethyl ether (2x50ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a brown oil. Purification on flash silica eluted with 100% hexane up to 5% EtOAC in hexane afforded a colourless oil (1.1g). ^1H NMR (250MHz. $CDCl_3$) δ 2.61-2.71 (1H, dd), 3.14-3.25 (1H, dd), 4.17-4.27 (1H, m), 7.33-7.70 (5H, m).

DESCRIPTION 20

2-(2-Trifluoromethyl-phenyl)-4-trimethyl-silanyl-but-3-yn-1-ol

Using the chemistry described in *Chem Ber.* (1988), 121, 1315-1320, the oxirane of Description 19 was opened using the titanium complex chemistry to give the title compound. ^1H NMR (250MHz,$CDCl_3$) δ 0.19 (9H, s), 2.01-2.09 (1H, dd), 3.58-3.69 (1H, m), 3.78-3.88 (1H, m), 4.28-4.34 (1H, m), 7.34-7.41 (1H, t), 7.51-7.59 (1H, t), 7.60-7.66 (1H, d), 7.74-7.80 (1H, d).

The alcohol of Description 20 was taken through the series of steps described in Descriptions 1 to 5 to afford the corresponding diol intermediates:

DESCRIPTION 21

(a) 2-(2-Trifluoromethyl-phenyl)-but-3-yn-1-ol

^{1}H NMR (250MHz,$CDCl_3$) δ 2.34-2.45 (1H, m), 2.62 (1H, d), 3.94-4.22 (2H, m), 4.54-4.64 (1H, m), 7.62-7.94 (1H, t), 7.82-7.98 (2H, t+d), 8.04-8.13 (1H, d).

(b) *tert*-Butyldimethylsiloxy-2-(2-trifluoromethyl-phenyl)-but-3-yne

^{1}H NMR (250MHz, $CDCl_3$) δ 0.012 (6H, s), 0.86 (9H, s), 2.22 (1H, d, J=2.5Hz), 3.77-3.91 (2H, m), 4.21-4.27 (1H, m), 7.32-7.42 (1H, t), 7.52-7.61 (1H, t), 7.62-7.68 (1H, d), 7.78-7.84 (1H, d).

(c) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-trifluoromethyl-phenyl)-but-1-ynyl]-3-(4-fluorophenyl)-morpholin-2-ol

MS CI$^+$ 614 (M+1$^+$, 100%).

(d) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-trifluoromethyl-phenyl)-butyl)-3-(4-fluorophenyl)-morpholin-2-ol

Two products were observed from this hydrogenation. After isolation, by flash chromatography (eluant 10-20% ethyl acetate in hexane), the two pairs of isomers were carried thought the next two reactions individually.

Spot 1 higher R_f MS CI$^+$ m/z 618 (M+1$^+$, 100%)

Spot 2 lower R_f MS CI$^+$ m/z 618 (M+1$^+$, 100%).

(e) 4-Benzyl-2-(4-hydroxy-3-(2-trifluoromethyl-phenyl)-butyl)-3-(4-fluorophenyl)-morpholin-2-ol

MS CI$^+$ m/z 504 (M+1$^+$, 100%).

DESCRIPTION 22

2-(3-Trifluoromethyl-phenyl)oxirane

Prepared according to the method of Description 19 starting from α,α,α-trifluoro-*m*-tolualdehyde. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.75-2.83 (1H, m), 3.14-3.23 (1H, m), 3.89-3.96 (1H, m), 7.43-7.62 (4H, m).

DESCRIPTION 23

2-(3-Trifluoromethyl-phenyl)-4-trimethyl-silanyl-but-3-yn-1-ol

Using the chemistry described in *Chem. Ber.* (1988), 121, 1315-1320, the oxirane of Description 22 was opened using the titanium complex chemistry to give the title compound. ^{1}H NMR (250MHz, $CDCl_3$) δ 0.21 (9H, s), 1.88-1.95 (1H, t), 3.73-3.82 (2H, m), 3.92-3.99 (1H, m), 7.45-7.70 (4H, m).

The alcohol of Description 23 was taken through the series of steps described in Descriptions 1 to 5 to afford the corresponding diol intermediates:

DESCRIPTION 24

(a) 2-(3-Trifluoromethyl-phenyl)-but-3-yn-1-ol

^{1}H NMR (250MHz, $CDCl_3$) δ 1.95-2.04 (1H, m), 2.41 (1H, d, J=2.5Hz) 3.78-3.87 (2H, m), 3.90-3.99 (1H, m), 7.44-7.70 (4H, m).

(b) *tert*-Butyldimethylsiloxy-2-(3-trifluoromethyl-phenyl)-but-3-yne

^{1}H NMR (250MHz, $CDCl_3$) δ 0.01 (6H, s), 0.89 (9H,s), 2.39 (1H, d, J=2.5Hz), 3.73-3.81 (1H, m), 3.87-3.95 (1H, m), 3.97-4.04 (1H, m), 7.48-7.76 (4H, m).

c) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-trifluoromethyl-phenyl)-but-1-ynyl]-3-(4-fluorophenyl)-morpholin-2-ol

MS CI+ m/z 614 (M+1+, 100%).

(d) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(3-trifluoromethyl-phenyl)-butyl]-3-(4-fluorophenyl)-morpholin-2-ol

No useful separation between isomers was seen at this stage. MS CI+ m/z 618 (M+1+, 100%).

(e) 4-Benzyl-2-(4-hydroxy-3-(3-trifluoromethyl-phenyl)-butyl)-3-(4-fluorophenyl)-morpholin-2-ol

MS CI+ m/z 504 (M+1+, 100%).

DESCRIPTION 25

2-(2-Trifluoromethoxy-phenyl)oxirane

Prepared according to the method of Description 19 starting from α,α,α-trifluoromethoxy-*o*-benzylaldehyde and purified by distillation Bp_{7mm} 60°C. ^1H NMR (250MHz, $CDCl_3$) δ 2.67-2.74 (1H, m), 3.16-3.24 (1H, m), 4.14-4.20 (1H, m), 7.20-7.38 (4H, m).

DESCRIPTION 26

2-(2-Trifluoromethyl-phenyl)-4-trimethyl-silanyl-but-3-yn-1-ol

Using the chemistry described in *Chem. Ber.* (1988) **121**, 1315-1320, the oxirane of Description 25 was opened using the titanium complex chemistry to give the title compound. ^1H NMR (250MHz, $CDCl_3$) δ 0.21 (9H, s), 1.93-2.01 (1H, m), 3.58-3.86 (2H, m), 4.25-4.31 (1H, m), 7.23-7.38 (3H, m), 7.61-7.67 (1H, m).

The alcohol of Description 26 was taken through the series of steps described in Descriptions 1 to 5 to afford the corresponding diol intermediates:

DESCRIPTION 27

(a) 2-(2-Trifluoromethyl-phenyl)-but-3-yn-1-ol

^{1}H NMR (250MHz, $CDCl_3$) δ 2.03-2.09 (1H, m), 2.45 (1H, d, J=2.5Hz), 3.62-3.70 (2H, m), 4.26-4.30 (1H, m), 7.29-7.42 (3H, m), 7.60-7.68 (1H, m).

(b) *tert*-Butyldimethylsiloxy-2-(2-trifluoromethoxy-phenyl)-but-3-yne

^{1}H NMR (360MHz, $CDCl_3$) δ 0.01 (6H, s), 0.87 (9H, s), 2.24 (1H, d, J=2.5Hz), 3.81-3.84 (2H, m), 4.20-4.25 (1H, m), 7.24-7.33 (3H, m), 7.66-7.70 (1H, m).

(c) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-trifluoromethoxy-phenyl)-but-1-ynyl]-3-(4-fluorophenyl)-morpholin-2-ol

MS CI$^+$ m/z 630 (M+1$^+$, 100%).

(d) 4-Benzyl-2-[4-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-trifluoromethoxy-phenyl)-butyl]-3-(4-fluorophenyl)morpholin-2-ol

MS CI$^+$ m/z 634 (M+1$^+$, 100%).

(e) 4-Benzyl-2-(4-hydroxy-3-(2-trifluoromethoxy-phenyl)-butyl)-3-(4-fluorophenyl)-morpholin-2-ol

MS CI$^+$ m/z 520 (M+1$^+$, 20%).

DESCRIPTION 28

4-Hydroxymethyl-N-(ρ-toluenesulfonyl)imidazole

4-Hydroxymethylimidazole hydrochloride (10g) was suspended in dichloromethane (200ml). ρ-Toluenesulfonyl chloride (15.58g) was added and triethylamine (25.8ml) was added dropwise to the stirred reaction mixture which was allowed to stir at room temperature overnight. The mixture was washed with water (2 x 100ml) and brine (1 x 100ml) and the

organic layer was dried and evaporated to leave a clear oil which was recrystallised from ethyl acetate/hexane to afford the title compound as a white crystalline solid (15g, 80%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.44 (3H, s), 4.55 (2H, s), 7.21 (1H, s), 7.35 (2H, d, J=8.0Hz), 7.62 (2H, d, J=8.0Hz), 7.98 (1H, s). MS (CI^+) m/z 253 (M+H, 100%).

DESCRIPTION 29

((N-p-Toluenesulfonyl)imidazol-2-yl)methyl methanesulfonate

The product of Description 28 (1g) was dissolved in dichloromethane (15ml) and the solution was cooled in an ice-methanol bath. Triethylamine (0.4g) was added dropwise in dichloromethane (1ml) followed by methanesulfonyl chloride (0.45g). The mixture was washed with water (2 x 10ml) and brine (1 x 10ml) and the organic layer was dried and evaporated to give the title compound as a white crystalline powder (1.3g). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.45 (3H, s), 3.00 (3H, s), 5.13 (2H, s), 7.39 (2H, d, J=8.0Hz), 7.40 (1H, s), 7.84 (2H, d, J=8.0Hz), 8.00 (1H, s). MS (CI^+) m/z 267 ($(M-CH_3O)^+$, 30%).

EXAMPLE 1

(2S,3S,9R)-4-Aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane (Isomer A)

The diol described in Description 5 (5g) was suspended in hydrochloric acid (200ml) and methanol was added to aid dissolution (50ml). The resulting mixture was heated at reflux for 2h. TLC (25% ethyl acetate in hexane) confirmed all starting material had reacted to give a mixture of 4 products. Hydrochloric acid was removed *in vacuo* and the residue was treated with sodium bicarbonate solution. The mixture was extracted with ethyl acetate (x3) and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford a yellow oil. This oil was purified on silica using 1-5% ethyl acetate in hexane as eluant. This removed Isomer A, the first component to elute, which was

recrystallised from isopropanol to afford the title compound as white crystals. MS CI$^+$ m/z 400 (M+1$^+$, 100%).

EXAMPLE 2

(2S,3S,9S)-4-Aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane (Isomer B1)

The second fraction to elute from the column described in Example 1 comprised a 1:1 mixture of isomers, inseparable by chromatography. The mixture was separated by fractional crystallisation from isopropanol to afford the title compound as colourless needles. MS CI$^+$ m/z 400 (M+1$^+$, 100%).

EXAMPLE 3

(2R,3S,9S)-4-Aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane (Isomer B2)

The mother liquors from the crystallisation described in Example 2 were concentrated and recrystallised from isopropanol (x2) to afford the title compound as colourless prisms. MS CI$^+$ m/z 400 (M+1$^+$, 100%).

EXAMPLE 4

(2R,3S,9R)-4-Aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane (Isomer C)

The third fraction to elute from the column described in Example 1 was concentrated to afford the title compound as a colourless oil. MS CI$^+$ m/z 400 (M+1$^+$, 100%).

EXAMPLE 5

(2S,3S,9R)-4-Aza-1,7-dioxa-3,9-diphenylspiro[5.5]undecane

The product of Example 1 (Isomer A) (0.2g) was dissolved in ethyl acetate with HCl (50ml), wetted palladium on carbon (20%) (120mg) was added and the reaction placed under an atmosphere of hydrogen, 40psi. When TLC (20% ethyl acetate in petrol) showed no starting material the

catalyst was removed *in vacuo*. The resultant yellow oil was purified on flash silica eluted with 20% ethyl acetate in petrol going up to 10% methanol in ethyl acetate to afford the title compound. MS CI$^+$ m/z 310 (M+1$^+$, 100%). ^{1}H NMR (360MHz, DMSO) HCl salt δ 1.22-1.33 (1H, m), 1.59-1.68 (1H, m), 1.77-1.86 (1H, m), 1.90-2.04 (1H, m), 2.46-2.58 (1H, m), 3.16 (1H, s), 3.22-3.37 (2H, m), 3.60-3.68 (1H, t), 3.71-3.79 (1H, m), 3.87-3.96 (1H, m), 3.96-4.08 (1H, m), 4.5 (1H, s), 7.18-7.32 (5H, m), 7.41-7.51 (3H, m), 7.55-7.62 (2H, m).

EXAMPLE 6

(2S,3S,9S)4-Aza-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane

The product of Example 2 (Isomer B1) (0.44g) was dissolved in methanolic ethyl acetate, wetted palladium on carbon (10%) (0.2g) was added and the reaction put under an atmosphere of hydrogen 40psi overnight. The catalyst was removed by filtration to afford the title compound as a white crystalline solid upon evaporation. MS CI$^-$ m/z 310 (M+1$^+$, 100%). ^{1}H NMR (360MHz, DMSO) δ 1.07-1.19 (1H, m), 1.38-1.47 (2H, m), 2.18-2.31 (1H, m), 2.82 (1H, br s), 3.26-3.36 (2H, m), 3.89-4.10 (4H. m), 4.42 (1H, s), 6.91-7.05 (5H, m), 7.42-7.49 (3H, m), 7.52-7.60 (2H, m).

EXAMPLE 7

(2S,3S,9S)-4-Aza-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane-4-ylmethyl)-2,4-dihydro-1,2,4-triazol-3-one

The compound of Example 6 (0.25g) was suspended in N,N´-dimethylformamide (2.6ml) with potassium carbonate (0.3g) and N-methylcarboxy-2-chloroacetamidrazone (see EP-0577394-A) (0.134g) and heated at 70°C for one hour. The dark yellow mixture was heated to 140°C to effect cyclisation. TLC in 5% methanol in ethyl acetate showed a good separation between the starting material, the acyclic and cyclic products. The mixture was diluted with water (30ml) and ethyl acetate

(10ml). The organic layer was washed with water (2 x 30ml), brine, dried ($MgSO_4$) and evaporated to afford a dark yellow semi-solid. Trituration with dichloromethane gave the title compound as a buff coloured crystalline solid (0.1g). MS CI^+ m/z 407 ($M+1^+$, 100%). ^1H NMR (360MHz, DMSO) HCl salt δ 1.22-1.34 (3H, m), 2.16-2.30 (1H, m), 2.33-2.44 (1H, m), 2.66-2.82 (3H, m), 3.25 (1H, s), 3.28-3.36 (1H, m), 3.60-3.67 (1H, m), 3.72-3.79 (1H, m), 3.87-4.00 (2H, m), 6.81-6.91 (4H, m), 6.94-7.00 (1H, m), 7.33 (3H, br s), 7.5 (1H, br s), 11.18-11.27 (2H, m).

EXAMPLE 8

4-Aza-4-benzyl-1,7-dioxa-3,8-diphenyl-spiro[5.4]decane

The diol described in Description 9 (0.16g) was dissolved in anhydrous ether, boron trifluoride etherate was added dropwise, which formed a gummy solid on contact. Dichloromethane was added to aid dissolution, the reaction was left stirring overnight. The ether was removed *in vacuo* and the boron complex was destroyed by stirring overnight in methanolic hydrogen chloride. The methanol was removed *in vacuo* to afford the title compound as a brown oil. MS CI^+ m/z 386 ($M+1^+$, 100%).

EXAMPLE 9

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-phenylspiro[5.4]decane

(a) (2R,3S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-phenylspiro[5.4]dec-9-ene

The enol triflate of Description 14 (240mg, 0.51mmol) was dissolved in anhydrous 1,2-dimethoxyethane (1.75ml) under an inert atmosphere. Sodium bicarbonate solution (0.76ml of a 2.0M solution, 1.52mmol) was added followed by phenylboronic acid (87mg, 0.71mmol), lithium chloride (64mg, 1.52mmol) and tetrakis(triphenylphosphine)palladium (0) (29mg, 0.025mmol) and the resulting mixture heated at reflux for 1½hours. The

reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (20ml) and water (20ml). The organic fraction was washed with water (2x20ml) and brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo* to a brown gum which was further purified by flash silica gel chromatography eluting with 10% ethyl acetate in hexane to yield the title compound as a white solid (152mg, 75%).

^1H NMR (360MHz, $CDCl_3$) δ 2.38 (1H, ddd, J=3.5, 12, 12), 2.83 (2H, m), 3.61 (1H, s), 3.73 (2H, m), 4.31 (2H, m), 4.97 (1H, dd, J=2, 13), 5.92 (1H, t, J=2), 6.92 (1H, t, J=8.8), 7.12 (2H, m), 7.25 (9H, m), 7.53 (2H, brm); MS (ES^+) m/z 402 (M+1, 100%).

(b) (2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-phenylspiro[5.4]decane

The alkene of step (a) (90mg, 0.22mmol) was hydrogenated overnight at 40psi in methanol (15ml) and chloroform (16μl) over 10% palladium on charcoal (0.15g). The catalyst was removed by filtration through a pad of Hyflo™, and the solvent evaporated. The residue was partitioned between dilute sodium bicarbonate (20ml) and ethyl acetate (20ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Further purification by flash silica gel chromatography eluting with 50-100% ethyl acetate in hexane, afforded the title compound as a colourless oil (61mg, 87%).

^1H NMR (500MHz, $CDCl_3$) δ 1.71 (1H, dd, J=10.2, 12.7), 2.22 (1H, m), 3.04 (1H, dd, J=2.2, 12.3), 3.19 (1H, m), 3.62 (3H, m), 4.10 (1H, s), 4.21 (1H, m), 4.34 (1H, t, J=8), 6.77 (2H, dd, J=1.8, 8.1), 7.03 (2H, t, J=8.7), 7.13 (3H, m), 7.49 (2H, dd, J=5.6, 8.7); MS (ES^+) m/z 314 (M+1, 100%).

EXAMPLE 10

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl) spiro[5.4]decane

(a) (2S,3S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl)spiro[5.4]dec-9-ene

The title compound was obtained from the boronic acid of Description 15 (288mg, 1.90mmol) according to the method of Example 9, step (a), as a pale yellow foam (181mg, 66%).

^{1}H NMR (250MHz, $CDCl_3$) δ 2.38 (1H, ddd, J=3.5, 12,12), 2.82 (2H, m), 3.62 (1H, s), 3.78 (3H, s), 3.8-3.7 (2H, m), 4.32 (2H, m), 4.98 (1H, dd, J=2, 12.9), 6.15 (1H, t, J=2), 6.96-6.80 (5H, m), 7.13-7.18 (6H, m), 7.54 (2H, brs); MS (ES^+) m/z 432 (M+1, 100%).

(b) (2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl) spiro[5.4]decane

The alkene of step (a) (200mg, 0.46mmol) was dissolved in warm methanol (5ml) and degassed with nitrogen for 5-10 minutes. Ammonium formate (500mg) and 10% palladium on charcoal (100mg) were added, the reaction flask purged with nitrogen, and the resulting suspension heated at reflux for 2-24 hours. The cooled reaction mixture was filtered through a pad of Hyflo™, and concentrated *in vacuo* to a crude gum which was purified by flash silica gel chromatography eluting with 67-100% ethyl acetate in hexane (or 4-8% methanol in dichloromethane) to yield the title compound as a colourless oil (80mg, 51%).

^{1}H NMR (250MHz, $CDCl_3$) δ 1.80 (1H, m), 2.08 (1H, m), 3.03 (1H, dd, J=2, 12), 3.20 (1H, ddd, J=3.6, 12, 12), 3.65-3.55 (5H, m), 3.96 (1H, m), 4.01 (1H, s), 4.23 (1H, m), 4.33 (1H, t, J=8), 6.72-6.64 (3H, m), 7.26-6.97 (3H, m), 7.49 (2H, m); MS (ES^+) m/z 344 (M+1, 100%).

EXAMPLE 11

(2S,3S,9S)-4-Aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl)spiro[5.4]decane

The title compound was obtained from the compound of Example 10 (70mg, 0.2mmol) according to the method of Example 7 as white needles (50mg, 56%). Mp 237-238°C (toluene).

^{1}H NMR (250MHz, $CDCl_3$) δ 1.90 (1H, m), 2.12 (1H, m), 2.54 (1H, m), 2.89 (2H, m), 3.67-3.48 (7H, m), 3.89 (1H, m), 4.20 (1H, m), 4.35 (1H, t, J=8), 6.57 (1H, m), 6.73 (2H, m), 7.19-7.01 (3H, m), 7.59 (2H, brs), 9.9 (1H, s), 10.6 (1H, s); MS (ES^+) m/z 441 (M+1, 100%).

EXAMPLE 12

(2R,3S,8R)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane (Isomer A) and (2R,3S,8S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane (Isomer B)

The diol of Description 18 (2.4g, 5.7mmol) was heated at reflux in a solution of 6N hydrochloric acid (127ml) and methanol (38ml) for 18 hours. The methanol was evaporated *in vacuo* and the aqueous residue neutralised to pH 7-8 with sodium carbonate. The resulting solution was extracted with ethyl acetate (3x200ml), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to an orange oil (3.0g). The crude concentrate was purified by flash silica gel chromatography eluting with 8-20% ethyl acetate in hexane to yield the separated title compounds as viscous oils which solidified on standing (1.05g total, 46%).

Isomer A:- R_f 0.29 (10% ethyl acetate in hexane);

Analysis: $C_{26}H_{26}FNO_2$ requires C, 77.57; H, 6.50; N, 3.47;

Found: C, 77.16; H, 6.38; N, 3.37%);

^{1}H NMR (360MHz, $CDCl_3$) δ 1.77-2.00 (3H, m), 2.34 (1H, dt, J=11.9, 3.5Hz), 2.78 (2H, d, J=13.2Hz), 3.49 (1H, s), 3.65 (1H, d, J=13.3Hz), 3.64-3.69 (1H, m), 4.38 (1H, dt, J=11.7, 2.4Hz), 4.46 (1H, dd, J=8.9, 5.6Hz), 7.04 (2H, t, J=8.8Hz), 7.17-7.35 (10H, m), 7,63 (2H, br s); MS (ES^+) 404 (M+1, 100%).

Isomer B:- R_f 0.24 (10% ethyl acetate in hexane);

^{1}H NMR (250MHz, $CDCl_3$) δ 1.08-1.17 (1H, m), 1.90-2.21 (3H, m), 2.33

(1H, dt, J=11.9, 3.5Hz), 3.11 (2H, d, J=13.8Hz), 3.54 (1H, s), 3.55-3.60 (1H, m), 3.70 (1H, d, J=13.3Hz), 4.23 (1H, dt, J=11.7, 2.5Hz), 4.98 (1H, dd, J=8.4, 6.7Hz), 7.01-7.08 (4H, m), 7.15-7.33 (8H, m), 7.65 (2H, br s); MS (ES^+) 404 (M+1, 100%).

EXAMPLE 13

(2R,3S,8R)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane hydrochloride

Isomer A of Example 12 (303mg, 0.75mmol) was dissolved in methanol (15ml) and chloroform (2μl, 0.25mmol), and hydrogenated at 40psi with 10% palladium on charcoal (200mg) for 4 hours. The solution was filtered through a pad of Hyflo™, concentrated to dryness *in vacuo* and the residual solid (234mg) recrystallised to give the title compound as a white solid (100mg). m.p. 260-261°C (dec.) (methanol-ethyl acetate).

Analysis: $C_{19}H_{20}FNO_2.HCl.0.3H_2O$ requires C, 64.24; H, 6.13; N, 3.94;
Found: C, 64.19; H, 5.95; N, 3.84%.

^1H NMR (360MHz, d_6-DMSO) δ 1.60-1.70 (1H, m), 1.78-1.94 (1H, m), 1.98-2.10 (2H, m), 3.25-3.32 (2H, m), 3.96 (1H, br d, J=11.9Hz), 4.30 (1H, m), 4.69-4.74 (1H, m), 4.74 (1H, s), 7.30-7.39 (7H, m), 7.70 (2H, dd, J=8.7, 5.5Hz), 9.5-9.8 (~1H, vbr s), 9.9-10.3 (~1H, vbr s); MS (ES^+) 314 (M+1, 100%).

EXAMPLE 14

(2R,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane hydrochloride

The title compound was prepared from Isomer B of Example 12 (455mg, 1.13mmol) according to the method of Example 13 to give, after recrystallisation, a white solid (194mg). m.p. 234-235°C (dec.) (methanol-ethyl acetate).

Analysis: $C_{19}H_{20}FNO_2.1.35HCl$ requires C, 62.94; H, 5.94; N, 3.86;
Found: C, 62.96; H, 5.71; N, 3.93%.

^{1}H NMR (360MHz, d_6-DMSO) δ 1.00-1.11 (1H, m), 1.97 (2H, m), 2.24 (1H, sextet, J=6.3Hz), 3.26-3.32 (2H, m), 3.89 (1H, d, J=11.7Hz), 4.21 (1H, m), 4.75 (1H, s), 5.05 (1H, dd, J=8.7, 6.5Hz), 7.20 (2H, d, J=7.9Hz), 7.26-7.35 (5H, m), 7.71 (2H, dd, J=8.7, 5.4Hz), 9.6-10.3 (~2H, vbr s); MS (ES^+) 314 (M+1, 100%).

EXAMPLE 15

(2R,3S,8R)-4-Aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane

The title compound was prepared from the product of Example 13 (192mg, 0.55mmol) according to the method of Example 7 as a foam (80mg, 35%).

Analysis: $C_{22}H_{23}FN_4O_3.H_2O$ requires C, 61.67; H, 5.88; N, 13.08;
Found: C, 61.75; H, 5.74; N, 12.28%

^{1}H NMR (360MHz, $CDCl_3$) δ 1.65-1.76 (1H, m), 1.82-2.01 (3H, m), 2.56 (1H, br t, J=11.6Hz), 2.79 (1H, d, J=11.2Hz), 2.90 (1H, d, J=14.6Hz), 3.38 (1H, d, J=14.6Hz), 3.55 (1H, s), 3.73 (1H, br d, J=9.4Hz), 4.38 (1H, br t, J=11.7Hz), 4.52 (1H, dd, J=9.1, 6.3Hz), 7.05 (2H, t, J=8.6Hz), 7.25-7.34 (5H, m), 7.54 (2H, br s), 9.46 (1H, s), 9.92 (~1H, br s); MS (ES^+) 411 (M+1, 100%).

EXAMPLE 16

(2R,3S,8S)-4-Aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane

The title compound was prepared from the product of Example 14 (284mg, 0.81mmol) according to the method of Example 7 as a foam (86mg, 26%).

Analysis: $C_{22}H_{23}FN_4O_3.0.5H_2O$ requires C, 63.00; H, 5.77; N, 13.86;
Found: C, 63.05; H, 5.53; N, 13.14%.

^{1}H NMR (360MHz, $CDCl_3$) δ 1.10-1.16 (1H, m), 1.90-1.97 (~2H, m), 2.09-2.17 (1H, sextet, J=6.4Hz), 2.51 (1H, dt, J=11.9Hz, 3.5Hz), 2.77 (1H, d,

J=11.2Hz), 2.87 (1H, d, J=14.5Hz), 3.42 (1H, d, J=14.5Hz), 3.56 (1H, s), 3.63 (1H, br d, J=11.4Hz), 4.21 (1H, br t, J=11.7Hz), 5.00 (1H, t, J=7.5Hz), 7.01-7.07 (5H, m), 7.21-7.26 (4H, m), 7.56 (2H, br s), 9.64 (1H, s), 10.23 (~1H, br s); MS (ES^+) 411 (M+1, 100%).

EXAMPLE 17

4-Aza-4-benzyl-7-dioxa-5-phenyl-9-(2-trifluoromethyl-phenyl)-spiro[5.5]undecane (4 isomers)

The 2 pairs of isomers carried through from Description 21, steps (d) and (e), were cyclised separately according to the method of Example 1, each giving 2 isomers. After separation on flash silica, eluant 1-5% ethyl acetate in hexane, the 4 isomers were isolated. The product of Description 21 (d) spot 1 (2.32g) was cyclised to afford:

Spot 1 higher R_f (0.25g) (2R,3S,9R) MS CI^+ m/z 485 ($M+1^+$, 100%)

Spot 2 lower R_f (1.1g) (2S,3S,9R) MS CI^+ m/z 485 ($M+1^+$, 100%)

The product of Description 21 (d) spot 2 (1.91g) was cyclised to afford:

Spot 1 higher R_f (0.28g) (2S,3S,9S) MS CI^+ m/z 485 ($M+1^+$, 100%)

Spot 2 lower R_f (0.8g) (2R, 3S, 9S) MS CI^+ m/z 485 ($M+1^+$, 100%)

The four isomers were debenzylated (to give Examples 18-21) using the procedure described in Example 5 with final purification of each isomer on flash silica, eluting with 1% methanol in dichloromethane:

EXAMPLE 18

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl)spiro[5.5]undecane

The hydrochloride salt recrystallised from ethyl acetate. MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.21-1.38 (2H, m) 1.48-1.58 (1H, m), 2.18-2.32 (1H, m), 3.12 (1H, br s), 3.24-3.36 (2H, m), 3.86-4.10 (3H, m), 4.12-4.19 (1H, m), 4.55 (1H, br s), 7.00-7.06 (1H, m), 7.10-7.16 (1H, m), 7.30-7.45 (3H, m), 7.58-7.62 (1H, m), 7.67-7.74 (2H, m).

EXAMPLE 19

(3R,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl)spiro[5.5]undecane

The hydrochloride salt was recrystallised from ethyl acetate. MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.32-1.44 (1H, m), 1.61-1.70 (2H, m), 2.01-2.09 (1H, m), 2.96-3.04 (1H, m), 3.08-3.30 (2H, m), 3.65-3.74 (1H, m), 3.75-3.86 (1H, m), 4.00-4.10 (2H, m), 4.58-4.63 (1H, m), 7.29-7.36 (2H, m), 7.41-7.52 1H, m), 7.54-7.84 (5H, m), 9.58 (1H, br s).

EXAMPLE 20

(2R,3S,9R)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl)-phenyl)spiro[5.5]undecane

The hydrochloride salt was recrystallised from ethyl acetate/hexane. MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.31-1.52 (2H, m), 1.58-1.68 (1H, m), 2.02-2.14 (1H, m), 3.01-3.08 (1H, m), 3.15-3.31 (2H, m), 3.94-4.06 (2H, m), 4.08-4.19 (2H, m), 4.90 (1H, s), 7.30-7.40 (2H, t), 7.41-7.48 (1H, m), 7.49-7.56 (1H, m), 7.65-7.71 (1H, m), 7.82-7.89 (3H, m), 9.79 (1H, br s).

EXAMPLE 21

(2S,3S,9R)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl)-phenyl)spiro[5.5]undecane

The hydrochloride salt was recrystallised from ethyl acetate and methanol. MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.15-1.27 (1H, m), 1.55-1.65 (1H, m), 1.81-1.88 (1H, m), 1.98-2.13 (1H, m), 2.72-2.84 (1H, m), 3.26-3.32 (2H, m), 3.63-3.71 (1H, m), 3.77-3.86 (1H, m), 3.92-4.10 (2H, m), 4.58 (1H, s), 7.29-7.38 (2H, m), 7.42-7.48 (1H, m), 7.54-7.71 (5H, m), 9.95 (1H, br s).

EXAMPLE 22

(2S,3S,9S)-4-Aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl) spiro[5.5]undecane

(a) (2S,3S,9S)-4-Aza-4-(4-chlorobut-2-ynyl)-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl)spiro[5.5]undecane

1,4-Dichloro-2-butyne (0.071ml) and potassium carbonate (65mg) were stirred with anhydrous N'N'-dimethylformamide (2ml) under nitrogen atmosphere. The reaction was heated to 50°C, and the product of Example 18 (63mg) was added dropwise as a solution in N'N'-dimethylformamide. After 3 hours, the reaction mixture was dispersed between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent evaporated to afford a yellow oil. Purification on flash silica, eluting with 10-20% ethyl acetate in hexane afforded the title compound as a colourless oil (60mg).

(b) (2S,3S,9S)-4-Aza-4-(4-azidobut-2-ynyl)-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl)spiro[5.5]undecane

The chloroalkyne of step (a) above (60mg) was dissolved in dimethyl sulphoxide (3ml) and sodium azide (10mg) was added and stirred at room temperature for 3 hours. The reaction mixture was dispersed between ammonium chloride/ethyl acetate (4:1). The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound (55mg). MS CI^+ 534 ($M+1^+$, 100%); ^1H NMR (360MHz, $CDCl_3$) δ 1.26-1.56 (3H, m), 2.20 (6H, s), 2.28-2.40 (1H, m), 2.54 (1H, m), 2.89-2.96 (1H, d, J=11Hz), 3.09-3.15 (1H, br s), 3.25 (1H, d, J=14Hz), 3.30 (1H, s), 3.41-3.49 (2H, m), 3.64-3.76 (2H, m), 3.84-3.90 (1H, m), 4.01-4.09 (1H, m), 4.14-4.20 (1H, m), 6.91-6.96 (1H, m), 7.40-7.19 (5H. m), 7.26 (1H, s), 7.49-7.53 (1H, m).

c) (2S,3S,9S)-4-Aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethyl-phenyl) spiro[5.5]undecane

The azide of step (b) (60mg) was dissolved in dioxane (2ml) and cooled to 0°C under a blanket of nitrogen in a sealed tube. Dimethylamine (2ml) was condensed into the solution and the tube was sealed tightly. The sealed tube was heated at 60°C for 6 hours. By TLC (5% methanol in dichloromethane) no starting material remained. The solvent was removed *in vacuo* to afford a brown oil. This was purified by flash chromatography eluting with 5% methanol; 0.2% ammonia in dichloromethane to give the title compound. ^1H NMR (360MHz, $CDCl_3$) δ 1.26-1.56 (3H, m), 2.20 (6H, s), 2.28-2.40 (1H, m), 2.54 (1H, m), 2.89-2.96 (1H, d, J=11), 3.09-3.15 (1H, bs), 3.25 (1H, d, J=14), 3.30 (1H, s), 3.41-3.49 (2H, m), 3.64-3.76 (2H, m), 3.84-3.90 (1H, m), 4.01-4.09 (1H, m), 4.14-4.20 (1H, m), 6.91-6.96 (1H, m), 7.04-7.19 (5H, m), 7.26 (1H, s), 7.49-7.53 (1H, m). MS CI^+ m/z 534 (M+1, 100%).

EXAMPLE 23

4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethyl-phenyl)-spiro[5.5]undecane (4 isomers)

The product of Description 24(e) was cyclised according to the method of Example 1 to give four isomers were isolated by flash chromatography, eluant 1-10% ethyl acetate in hexane. This efficiently separated spot 1 (highest R_f) and spot 4 (lowest R_f). Spots 2 and 3 were isolated by lobar chromatography (eluant 1-5% ethyl acetate in hexane) and crystalisation from isopropyl alcohol.

Spot 1 (2S,3S,9R). MS CI^+ m/z 486 ($M+1^+$, 100%); ^1H NMR (360MHz, d_6-DMSO, salt) δ 1.16-1.28 (1H, m), 1.62-1.71 (1H, m), 1.73-1.85 (1H, m), 1.84-2.03 (1H, m), 2.62-2.72 (1H, m), 3.16-3.54 (3H, m), 3.64-4.10 (5H, m), 4.62-4.72 (1H, m), 7.30-7.61 (13H, m).

Spot 2 (2R,3S,9S). MS CI^+ m/z 486 ($M+1^+$, 100%); ^1H NMR (500MHz, $CDCl_3$, free base) δ 1.20-1.32 (1H, m), 1.64-1.72 (1H, m), 1.77-1.83 (1H, m), 1.99-2.08 (1H, m), 2.38-2.47 (1H, m), 2.77-2.91 (2H, m), 3.21 (1H, d, J=14Hz), 3.38 (1H, d, J=14Hz), 3.66 (1H, s), 3.76-3.86 (3H, m), 4.08-4.13 (1H, m), 7.01-7.09 (1H, m), 7.20-7.51 (12H, m).

Spot 3 (2R,3S,9R). MS CI^+ m/z 486 ($M+1^+$, 100%); ^1H NMR (360MHz, $CDCl_3$, free base) δ 1.10-1.58 (4H, m), 2.28-2.46 (2H, m), 2.74-2.86 (3H, m), 3.16 (1H, s), 3.57-3.73 (2H, m), 3.96-4.14 (2H, m), 6.94-7.34 (13H, m).

Spot 4 (2S,3S,9S). MS CI^+ m/z 486 ($M+1^+$, 100%); ^1H NMR (360MHz, $CDCl_3$, free base) δ 1.12-1.26 (1H, m), 1.46-1.69 (2H, m), 2.20-2.32 (1H, m), 2.37-2.47 (1H, m), 2.81-2.92 (2H, m), 3.03 (1H, d, J=14Hz), 3.56 (1H, s), 3.62 (1H, d, J=14Hz), 3.78-3.87 (1H, m), 3.99-4.10 (2H, m), 4.27-4.35 (1H, m), 6.95-7.02 (2H, m), 7.17-7.42 (10H, m), 7.52 (1H, s).

The four isomers were debenzylated (to give Examples 24-27) using the procedure described in Example 5 with final purification of each isomer on flash silica eluting with 1% methanol in dichloromethane:

EXAMPLE 24

(2R,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethylphenyl)spiro[5.5]undecane

The hydrochloride salt was recrystallised from ethyl acetate and methanol. MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.28-1.39 (1H, m), 1.67-1.79 (2H, m), 1.06-2.01 (1H, m), 2.94-3.05 (2H, m), 3.21-3.32 (1H, m), 3.61 (1H, N-H), 3.70-3.79 (1H, t), 3.81-3.87 (1H, m), 4.00-4.12 (2H, m), 4.54 (1H, s), 7.30-7.38 (2H, t), 7.55-7.64 (4H, m), 7.78-7.85 (2H, m).

EXAMPLE 25

(2R,3S,9R)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethylphenyl)spiro[5.5]undecane

MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.15-1.28 (1H, m), 1.32-1.41 (1H, m), 1.49-1.62 (1H, m), 2.33-2.45 (1H, m), 2.85 (1H, s), 3.11-3.31 (2H, m), 3.74-3.84 (1H, m), 3.94 (1H, s), 4.06-4.14 (1H, m), 4.16-4.35 (2H, m), 6.94-7.09 (3H, m), 7.13-7.21 (1H, m), 7.22-7.35 (2H, m), 7.30-7.63 (2H, m).

EXAMPLE 26

(2S,3S,9R)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethylphenyl)spiro[5.5]undecane

MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.22-1.33 (1H, m), 1.64-1.73 (1H, m), 1.78-1.86 (1H, m), 1.90-2.04 (1H, m), 2.65-2.76 (1H, m), 3.24-3.36 (2H, m), 3.65-3.73 (1H, t), 3.78-3.84 (1H, m), 3.88-3.95 (1H, m), 3.97-4.07 (1H, m), 4.56 (1H, s), 7.28-7.37 (2H, t), 7.50-7.60 (4H, m), 7.62-7.69 (2H, m).

EXAMPLE 27

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethyl-phenyl)spiro[5.5]undecane

MS CI$^+$ m/z 396 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.04-1.15 (1H, m), 1.61-1.72 (2H, m), 2.11-2.22 (1H, m), 3.00-3.12 (2H, m), 3.18-3.22 (1H, m), 4.00-4.18 (4H, m), 4.57 (1H, s), 7.24-7.33 (2H, m), 7.44-7.52 (1H, m), 7.53-7.58 (1H, m), 7.59-7.66 (2H, m), 7.72-7.80 (2H, m), 9.74 (1H, br s), 9.91 (1H, br s).

EXAMPLE 28

(2S,3S,9S)-4-Aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-trifluoromethyl-phenyl) spiro[5.5]undecane

Using the same chemistry as described in Example 22, the product of Example 27 (0.21g) was taken through to the title compound (58mg). MS CI$^+$ m/z 534 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 1.08-1.19 (1H, m), 1.45-1.61 (2H, m), 2.21-2.36 (7H, m+$(CH_3)_2$), 2.42-2.49 (1H, m), 2.84-3.94 (2H, m), 3.47 (2H, dd, J=14Hz, J_1=14Hz), 3.81 (2H, m), 4.05-4.12 (2H, m), 4.21-4.28 (1H, m), 6.97-7.04 (2H, t), 7.26-7.32 (1H, m), 7.37-7.48 (4H, m), 7.60 (1H, m),

EXAMPLE 29

(2S,3S,9S)-4-Aza-4-benzyl-7-dioxa-5-phenyl-9-(2-trifluoromethoxy-phenyl)-spiro[5.5]undecane

Only one of the four possible isomers from the product of Description 27(e) was isolated by flash chromatography eluting with 1-5% ethyl acetate in hexane. The diol (4g) was cyclised according to the method of Example 1 to give:

spot 1 highest R_f (0.35g) (2S,3S,9S) MS CI$^+$ m/z 502 (M+1$^+$, 100%); ^{1}H NMR (360MHz, $CDCl_3$, free base) δ 1.22-1.60 (3H, m), 2.25-2.38 (2H,

m), 2.78-2.88 (2H, m), 3.01-3.06 (1H, m), 3.19 (1H, s), 3.58-3.65 (1H, m), 3.71-3.76 (1H, d, J=13Hz), 3.84-3.91 (1H, m), 3.99-4.15 (2H, m), 6.67-6.73 (1H, m), 6.91-6.96 (1H, m), 7.02-7.12 (3H, m), 7.20-7.33 (8H, m).

The rest of the isomers (2.9g) were taken on to be debenzylated as a mixture.

EXAMPLE 30

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethoxyphenyl)spiro[5.5]undecane

The title compound of Example 29 was debenzylated according to the method of Example 5. The hydrochloride salt recrystallised from ethyl acetate. MS CI$^+$ m/z 412 (M+1$^+$, 100%); ^{1}H NMR (360MHz, d_6-DMSO HCl salt) δ 0.81-0.89 (1H, m), 1.00-1.10 (1H, m), 1.21-1.26 (1H, m), 1.36-1.55 (2H, m), 2.19-2.32 (1H, m), 3.04-3.11 (1H, m), 3.33 (6H, s), 3.90-4.15 (4H, m), 4.51 (1H, s), 6.80-6.86 (1H, m), 7.03-7.05 (1H, m), 7.18-7.28 (2H, m), 7.35-7.41 (2H, m), 7.63-7.71 (2H, m).

EXAMPLE 31

4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethoxyphenyl) spiro[5.5]undecane

The mixture of isomers referred to in Example 29 after debenzylation showed 2 major isomers which were separated by Lobar chromatography with eluant 0.2% ammonia 0-2% methanol in dichloromethane. Two single isomers with stereochemistry undetermined in the 2 and 9 positions were obtained:

(a) Higher R_f. The free base recrystallised from diethyl ether/hexane. MS CI$^+$ m/z 411 (M+1$^+$, 100%); ^{1}H NMR (360MHz, $CDCl_3$) δ 1.22-1.33 (1H, m), 1.58-1.68 (1H, m), 1.84-2.09 (3H, m), 3.71-3.79 (1H, m), 3.10-3.21 (2H, m), 3.69-3.85 (4H, m), 3.96-4.04 (1H, m), 7.00-7.07 (2H, t), 7.19-7.36 (4H, m), 7.51-7.59 (2H, m).

(b) Lower R_f. The hydrochloride salt recrystallised from ethyl acetate and methanol. MS CI$^+$ m/z 411 (M+1$^+$, 100%); ^{1}H NMR (360MHz, $CDCl_3$ HCl salt) δ 1.36-1.47 (1H, m), 1.59-1.68 (1H, m), 1.73-1.81 (1H, m), 2.01-2.16 (1H, m), 2.90-3.01 (1H, m), 3.28-3.44 (2H, m), 3.64-3.72 (1H, t), 3.80-3.89 (2H, m), 4.11-4.17 (1H, s), 4.21-4.32 (1H, m), 7.09-7.17 (2H, t), 7.18-7.34 (4H, m), 7.69-7.75 (2H, m).

EXAMPLE 32

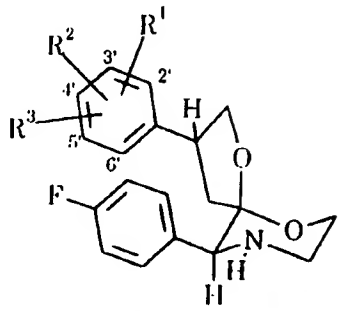
(2S,3S,9S)-4-Aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethoxyphenyl) spiro[5.5]undecane

Using the same chemistry as described in Example 22 the product of Example 30 (0.21g) was reacted to give the the title compound (90mg). MS CI$^+$ m/z 550 (M+1$^+$, 100%); ^{1}H NMR (360MHz, $CDCl_3$) δ 1.18-1.34 (3H, m), 1.41-1.49 (1H, m), 2.15-2.20 (6H, s), 2.24-2.38 (1H, m), 2.52-2.62 (1H, m), 2.88-2.94 (1H, m), 3.01-3.07 (1H, m), 3.20-3.26 (2H, m), 3.37-3.47 (2H, m), 3.63-3.74 (2H, m), 3.83-3.92 (1H, m), 4.01-4.16 (2H, m), 6.68-6.75 (1H, m), 6.96-7.12 (7H, m).

The following Examples (Table 1) were prepared according to the method of Example 9 from (2R,3S)-(4-aza-4-benzyl-1.7-dioxa-3-(4-fluorophenyl)-spiro[5.4]dec-9-en-9-yl) trifluoromethanesulfonate (Description 14) and the appropriate phenylboronic acid.

The following Examples (Table 2) were prepared according to the method of Example 22 from the corresponding Example from Table 1.

TABLE 1



Ex. No.	R^1	R^2	R^3	Data
33	3'-CF_3	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.71 (1H, m), 2.30 (1H, m), 3.05-3.26 (2H, m), 3.63 (3H, m), 4.05 (1H, s), 4.19-4.39 (2H, m), 6.89 (1H, m), 7.03 (3H, m), 7.20 (1H, m), 7.38 (1H, m), 7.48-7.54 (2H, m); MS (ES$^+$) m/z 381 (M+1, 100%).
34	2'-CF_3	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.64-1.91 (2H, m), 2.24-2.36 (1H, dd), 3.01-3.12 (1H, dt), 3.15-3.28 (1H, td), 3.62-3.76 (2H, m), 3.89-4.05 (2H, m), 4.10-4.25 (1H, td), 4.29-4.38 (1H, t), 6.27-6.46 (1H, m), 6.96-7.20 (4H, m), 7.42-7.58 (3H, m); MS (ES$^+$) m/z 382 (M+1, 100%).
35	4'-OCH_3	H	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.66 (1H, dd, J=12.7, 10.2), 1.87 (1H, bs), 2.16 (1H, dd, J=12.7, 7.5), 3.03 (1H, dd, J=12.3, 2.4), 3.18 (1H, dt, J=12.2, 3.6), 3.45-3.75 (3H, m), 3.72 (3H, s), 4.00 (1H, s), 4.21 (1H, dt, J=11.8, 2.9), 4.31 (1H, t, J=7.9), 6.69 (4H, s), 7.03 (2H, t, J=8.7), 7.48 (2H, m); MS (ES$^+$) m/z 344 (M+1, 100%), 326 (M-17, 25).
36	2'-CH_3	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.64 (1H, dd, J=12.8, 10.1), 1.97-2.21 (2H, m), 2.17 (3H, s), 2.96 (1H, dd, J=12.2, 2.2), 3.12 (1H, dt, J=12.2, 3.6), 3.49 (1H, t, J=8.0), 3.60 (1H, dd, J=10.3, 2.4), 3.70-3.87 (1H, m), 3.94 (1H, s), 4.14 (1H, dt, J=11.5, 3.0), 4.25 (1H, t, J=8.2), 6.38 (1H, m), 6.84-7.01 (4H, m), 7.24 (1H, m), 7.38-7.46 (2H, m); MS (ES$^+$) m/z 328 (M+1, 100%), 310 (M-17, 32).
37	2'-OCF_3	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.74 (1H, m), 2.25 (1H, m), 3.07 (1H, m), 3.25 (1H, m), 3.55-3.70 (2H, m), 3.83-3.94 (2H, m), 4.03 (1H, m), 4.34 (1H, m), 6.36 (1H, d, J=8.5Hz), 6.91-7.12 (5H, m), 7.47-7.52 (2H, m); MS (ES$^+$) m/z 397 (M+1, 100%).

Ex. No.	R^1	R^2	R^3	Data
38	3'-OCH_3	H	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.71 (1H, dd, J=12.8, 10.0), 2.20 (1H, dd, J=12.9, 7.5), 3.03 (1H, dd, J=12.3, 2.1), 3.18 (1H, dt, J=12.3, 3.6), 3.53-3.66 (3H, m), 3.67 (3H, s), 4.00 (1H, s), 4.21 (1H, dt, J=11.8, 3.0), 4.33 (1H, t, J=7.4), 6.32 (1H, t, J=2.0), 6.39 (1H, d, J=7.7), 6.65 (1H, dd, J=8.3, 2.5), 6.99-7.08 (3H, m), 7.47-7.52 (2H, m); MS (ES^+) m/z 344 (M+1, 100%).
39	3'-NH_2	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.74 (1H, m), 2.22 (1H, m), 3.06 (1H, m), 3.33 (1H, m), 3.50-3.68 (4H, m), 4.00 (1H, s), 4.08-4.35 (2H, m), 6.00 (1H, m), 6.21 (1H, d, J=7.61Hz), 6.45 (1H, m), 6.87-7.07 (3H, m), 7.49 (2H, m); MS (ES^+) m/z 328 (M+1, 100%).
40	3'-$OCH(CH_3)_2$	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.26 (6H, d, J=3.0), 1.65-1.75 (1H, m), 2.20 (1H, m), 3.01-3.25 (2H, m), 3.52-3.68 (3H, m), 4.00 (1H, s), 4.16-4.52 (3H, m), 6.29 (1H, m), 6.37 (1H, d, J=7.7Hz), 6.65 (1H, m), 6.99-7.07 (3H, m), 7.50 (2H, m).
41	2'-OCH_3	5'-F	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.76 (1H, dd, J=10, 12.5), 3.00-3.06 (1H, m), 3.19 (1H, td, J=3.5, 12), 3.56 (1H, t, J=7.7), 3.62 (3H, s), 3.60-3.68 (1H, m), 3.85-3.94 (1H, m), 4.00 (1H, s), 4.21 (1H, td, J=3.5, 12), 4.31 (1H, t, J=7.7), 6.29 (1H, dd, J=3, 9.5), 6.63 (1H, dd, J=4.5, 9), 6.76 (1H, td, J=3, 9.5), 7.00 (2H, t, J=8.7) 7.42-7.49 (2H, m); MS (ES^+) m/z 362 (M+1, 100%).
42	2'-OCH_3	5'-OCH_3	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.80 (1H, dd, J=11, 12), 2.08 (1H, dd, J=7.7, 12), 3.03 (1H, dd, J=2, 12), 3.18 (1H, dt, J=3.6, 12), 2.57 (1H, t, J=8), 3.59 (3H, s), 3.62 (3H, s), 3.6 (1H, dd, J=2, 12), 3.91 (1H, m), 4.11 (1H, s), 4.22 (1H, dt, J=3.6, 12), 4.32 (1H, t, J=8), 6.23 (1H, d, J=3), 6.61 (1H, dd, J=3, 8.5), 6.66 (1H, d, J=8.5), 6.99 (2H, t, J=8.6), 7.48 (2H, dd, J=5.5, 8.6); MS (ES^+) m/z 374 (M+1, 100%).
43	2'-$OCH(CH_3)_2$	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.14-1.30 (6H, m), 1.76 (1H, dd, J=10.6 and 12.5Hz), 2.11 (1H, dd, J=7.7 and 12.5), 2.21 (1H, brs), 3.04 (1H, dd, J=1.9 and 12.3), 3.19 (1H, ddd, J=3.6, 12.2 and 12.2), 3.54 (1H, dd, J=8 and 8), 3.67 (1H, dd, J=2.3 and 11.3), 3.93-4.04 (2H, m), 4.23 (1H, ddd, J=3.1, 11.8 and 11.8), 4.34-4.52 (2H, m), 6.56 (1H, dd, J=1.7 and 7.6), 6.69 (1H, dd, J=1.1 and 8.8), 6.74 (1H, d, J=7.8), 6.95-7.14 (3H, m), 7.44-7.53 (2H, m); MS (ES^+) m/z 372 (M+1, 100%).

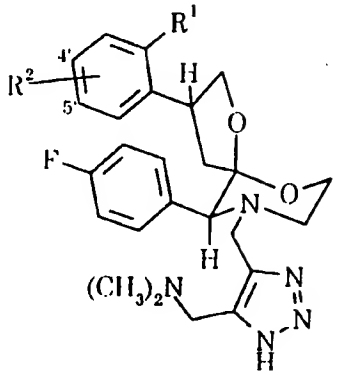
Ex. No.	R^1	R^2	R^3	Data
44	2'-$O(CH_2)_2CH_3$	H	H	^{1}H NMR (360MHz, d_6-DMSO) δ 0.92 (3H, t, J=7.5), 1.57 (2H, q, J=7.5), 1.73 (1H, t, J=10.8), 2.20 (1H, dd, J=7.5, 12.6), 3.2-3.3 (1H, m), 3.58 (1H, t, J=8.5), 3.76-3.90 (5H, m), 4.16-4.18 (1H, m), 4.32 (1H, t, J=8), 4.73 (1H, s), 6.58 (1H, d, J=6), 6.70 (1H, t, J=6.8), 6.86 (1H, d, J=7.5), 7.11 (1H, t, J=8), 7.30 (2H, t, J=9), 7.68 (2H, dd, J=5, 8); MS (ES^+) m/z 372 (M+1, 100%).
45	2'-$OCH(CH_3)_2$	5'-F	H	^{1}H NMR (250MHz, d_6-DMSO) δ 1.13 (6H, dd, J=6.1 and 6.1), 1.61-1.70 (1H, m), 2.26 (1H, dd, J=7.8 and 13.0), 3.20-3.40 (3H, m), 3.64 (1H, dd, J=7.9 and 7.9), 3.68-3.82 (1H, m), 3.84-3.94 (1H, m), 4.08-4.20 (1H, m), 4.28 (1H, dd, J=8.0 and 8.0), 4.42-4.54 (1H, m), 4.77 (1H, brs), 6.21 (1H, d, J=9.7), 6.89 (2H, d, J=5.0), 7.30 (2H, dd, J=8.8 and 8.8), 7.66 (2H, dd, J=5.5 and 8.7); MS (ES^+) m/z 371 (M+1, 100%).
46	2'-$OCH(CH_3)_2$	5'-$CH(CH_3)_2$	H	^{1}H NMR (250MHz, DMSO salt) δ 0.98-1.05 (3H, d, J=7), 1.09-1.17 (3H, m), 1.63-1.75 (1H, m), 2.14-2.26 (1H, m), 2.52-2.65 (1H, m), 3.24-3.40 (2H, m+H_2O), 3.50-3.58 (1H, m), 3.77-3.95 (2H, m), 4.12-4.34 (2H, m), 4.36-4.52 (1H, m), 4.75 (1H, s), 6.27-6.32 (1H, m), 6.77-6.68 (1H, m), 6.92-6.98 (1H, m), 7.30-7.40 (2H, m), 7.68-7.77 (2H, m); MS (ES^+) m/z 414 (M+1, 100%).
47	2'-OCH_3	5'-$CH(CH_3)_2$	H	^{1}H NMR (360MHz, DMSO) δ 1.02 (6H, d, J=6.9), 1.75 (1H, t, J=10.9), 2.15 (1H, m), 2.62 (1H, m), 3.27 (2H, m), 3.55 (3H, s), 3.57 (1H, t, J=8.2), 3.80 (1H, m), 3.87 (1H, m), 4.19 (1H, m), 4.28 (1H, t, J=8.3), 4.74 (1H, s), 6.40 (1H, d, J=2.2), 6.77 (1H, d, J=8.5), 6.97 (1H, dd, J=8.4, 2.2), 7.34 (2H, t, J=8.9), 7.71 (2H, m); MS (ES^+) m/z 386 (M+1, 100%).
48	2'-OCH_2CH_3	5'-F	H	^{1}H NMR (360MHz, DMSO) δ 1.18 (3H, t, J=7), 1.71 (1H, m), 2.25 (1H, m), 3.27 (2H, m), 3.64 (1H, t, J=7.8), 3.80 (1H, t, J=8.3), 3.89 (3H, m), 4.18 (1H, m), 4.29 (1H, t, J=8.2), 4.74 (1H, s), 6.27 (1H, dd, J=9.8, 3), 6.89 (2H, m), 7.28 (2H, t, J=8.9), 7.67 (2H, m); MS (ES^+) m/z 376 (M+1, 100%).
49	2'-OCH_3	5'-$C(CH_3)_3$	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.16 (9H, s), 1.88 (1H, m), 2.11 (1H, m), 3.07 (1H, m), 3.20 (1H, m), 3.57 (3H, s), 3.68 (2H, m), 3.88 (1H, m), 4.03 (1H, s), 4.20-4.34 (2H, m), 6.65 (1H, d, J=8.5), 6.76 (1H, d, J=2.5), 6.99-7.13 (3H, m), 7.52 (2H, m); MS (ES^+) m/z 399 (M+1, 100%).
50	2'-OH	H	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.82 (1H, t, J=10.9), 2.10 (1H, m), 3.06 (1H, dd, J=12.4, 2.1), 3.19 (1H, dt, J=12, 3.6), 3.56 (1H, t, J=8.3), 3.65 (1H, dd, J= 11, 2.8), 3.96 (1H, m), 4.03 (1H, s), 4.23 (1H, dt, J=11.8, 2.9), 4.37 (1H, t, J=8.2), 6.54 (2H, m), 6.72 (1H, dd, J=8, 1.0), 6.96 (3H, m), 7.50 (2H, m); MS (ES^+) m/z 330 (M+1, 100%).

Ex. No.	R^1	R^2	R^3	Data
51	2'-OCH_2CH_2-3'		H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.88 (1H, dd, J=11, 12), 2.07 (1H, dd, J=7.5, 12), 3.02 (1H, dd, J=2, 12), 3.09 (2H, t, J=8.5), 3.18 (1H, td, J=3.6, 12), 3.62 (1H, t, J=8.5), 3.62-3.73 (2H, m), 3.99 (1H, s), 4.22 (1H, td, J=3.6, 12), 4.24-4.39 (3H, m), 6.50 (1H, d, J=7.7), 6.62 (1H, t, J=7.5), 6.9-7.0 (3H, m), 7.4-7.5 (2H, m); MS (ES^+) m/z 356 (M+1, 100%).
52	2'-OCH_3	6'-F	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.87 (1H, m), 2.19 (1H, m), 3.05 (1H, m), 3.20 (1H, dt, J=3.5, 12.1), 3.43 (3H, s), 3.63-3.70 (2H, m), 3.86 (1H, m), 4.01 (1H, s), 4.12-4.28 (2H, m), 6.55 (2H, m), 7.03 (3H, m), 7.51 (2H, m); MS (ES^+) m/z 362 (M+1, 100%).
53	2'-CH_3	3'-F	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.65 (1H, m), 2.10 (3H, s), 2.24 (1H, m), 3.12 (1H, m), 3.25 (1H, m), 3.66 (1H, t, J=7.9), 3.72 (1H, m), 3.85 (1H, m), 4.22 (1H, d, J=9.8), 4.36 (1H, t, J=8.4), 4.50 (1H, t, J=10.2), 6.20 (1H, d, J=7.7), 6.78 (1H, t, J=8.4), 6.87 (1H, m), 7.04 (2H, m), 7.65 (2H, m), 9.97 (1H brs), 10.59 (1H, brs); MS (ES^+) m/z 346 (M+1, 100%).
54	3'-CH_3	5'-CH_3	H	^{1}H NMR (360MHz, DMSO) δ 1.61 (1H, m), 2.08 (6H, s), 2.33 (1H,m), 3.28 (2H, m), 3.52 (2H, m), 3.87 (1H, d, J=11.9), 4.16 (1H, m), 4.32 (1H, m), 4.74 (1H, s), 6.25 (2H, s), 6.73 (1H, s), 7.36 (2H, t, J=8.9), 7.72 (2H, m); MS (ES^+) m/z 342 (M+1, 100%).
55	2'-OCH_3	3'-OCH_3	H	HCl salt ^{1}H NMR (D_2O) δ 1.49 (1H, dd, J=16.0, 10.0), 2.06 (1H, dd, J=16.0, 10.0), 3.12 (2H, m), 3.33 (3H, s), 3.49 (3H, s), 3.66 (3H, m), 4.11 (2H, m), 4.40 (1H, s), 5.90 (1H, m), 6.57 (2H, m), 6.91 (2H, m), 7.30 (2H, m); MS (ES^+) m/z 374 (M+1, 100%).
56	2'-$C(O)N(CH_2CH_3)_2$	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 0.98-1.02 (3H, m), 1.22-1.28 (3H, m), 1.68-1.78 (1H, m), 2.01-2.32 (2H, m), 3.02-3.23 (4H, m), 3.40-3.46 (1H, m), 3.40-3.70 (4H, m), 4.01 (1H, s), 4.07-4.34 (2H, m), 6.34-6.42 (1H, m), 7.02-7.15 (5H, m), 7.42-7.56 (2H, m); MS (ES^+) m/z 413 (M+1, 100%).
57	2'-$OCH(CH_3)_2$	4'-F	5'-F	^{1}H NMR (250MHz, $CDCl_3$) δ 1.05-1.18 (6H, m), 1.89-2.11 (2H, m), 2.39 (1H, brs), 3.09 (1H, dd, J=2.2, 12.2), 3.18 (1H, ddd, J=3.5, 12, 12) 3.67 (1H, dd, J=5.9, 11.3), 3.91-3.93 (1H, m), 4.02 (1H, s), 4.07-4.35 (4H, m), 6.42-6.46 (1H, m), 6.80-6.91 (1H, m), 6.98-7.05 (2H, m), 7.44-7.50 (2H, m); MS (ES^+) m/z 408 (M+1, 100%).

Ex. No.	R^1	R^2	R^3	Data
58	2′-$S(O)_2N(CH_2CH_3)_2$	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.11 (6H, t, J=7.1), 1.69 (1H, dd, J=7.5, 13), 2.31 (1H, dd, J=8.5, 13), 2.90-3.07 (2H, m), 3.14-3.20 (1H, m), 3.27 (4H, dq, J=2.1, 7.2), 3.61-3.70 (2H, m), 4.02 (1H, s), 4.07-4.20 (2H, m), 4.31-4.48 (1H, m), 6.38-6.42 (1H, m), 7.03 (1H, dd, J=8.7), 7.12-7.16 (2H, m), 7.42-7.52 (2H, m), 7.69-7.76 (1H, m); MS (ES^+) m/z 449 (M+1, 100%).
59	2′-NH-$(CH_2)_3$-3′		H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.73-1.81 (2H, m), 1.90 (1H, bs), 2.08 (1H, dd, J=12.8, 8.3), 2.67 (2H, t, J=6.4), 2.88-2.95 (1H, m), 3.01-3.10 (2H, m), 3.18 (1H, dt, J=12.2, 3.6), 3.42 (1H, bs), 3.57 (1H, t, J=8.6), 3.64 (1H, dd, J=11.6, 2.9), 3.74 (1H, dd, J=8.5, 7.0), 4.02 (1H, s), 4.17 (1H, dt, J=11.8, 2.9), 4.25 (1H, t, J=8.6), 6.40 (1H, t, J=7.4), 6.49 (1H, dd, J=7.5, 1.3), 6.75 (1H, dd, J=6.7, 0.7), 7.00 (2H, m), 7.47 (2H, m); MS (ES^+) m/z 369 (M+1, 100%), 365 (12%).
60	2′-F	5′-F	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.72 (1H, dd, J=12.8, 9), 2.22 (1H, dd, J=10, 12.8), 3.04 (1H, dd, J=2, 12), 3.20 (1H, dt, J=3.6, 12), 3.58-3.71 (2H, m), 3.80-3.89 (1H, m), 4.00 (1H, s), 4.20 (1H, dt, J=3.6, 12), 4.33 (1H, t, J=8), 6.19 (1H, m), 6.70-6.89 (2H, m), 6.95-7.0 (2H, m), 7.43-7.52 (2H, m); MS (ES^+) m/z 350 (M+1, 100%).
61	2′-O-CH_2-O-3′		H	HCl salt ^{1}H NMR (d_6-DMSO) δ 1.65 (1H, dd, J=11.0, 8.0), 2.41 (1H, dd, J=11.0, 8.0), 3.46 (2H, m), 3.55-3.69 (2H, m), 3.97 (1H, m), 4.28 (1H, m), 4.44 (1H, m), 4.87 (1H, s), 6.05 (2H, s), 6.29 (1H, d, J=1.0), 6.30 (1H, dd, J=8.0, 1.0), 6.45 (1H, m), 7.46 (2H, m), 7.82 (2H, m); MS (ES^+) m/z 358 (M+1, 100%).
62	2′-OCH_3	5′-CF_3	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.82 (1H, dd, J=10, 12), 2.11 (1H, dd, J=8, 12), 3.04 (1H, dd, J=2, 12), 3.19 (1H, td, J=3.5, 12), 3.61 (1H, t, J=8), 3.67 (3H, s), 3.63-3.68 (1H, m), 3.92 (1H, mc), 4.01 (1H, s), 4.22 (1H, dt, J=3.5, 12), 4.32 (1H, t, J=8), 6.77 (1H, d, J=8), 6.90 (1H, d, J=2), 7.00 (2H, t, J=8.5), 7.36 (1H, dd, J=2, 8.5), 7.45-7.53 (2H, m); MS (ES^+) m/z 411 (M+1, 100%).
63	2′-$OCH(CH_3)_2$	4′-F	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.22 (6H, m), 1.73 (1H, m), 2.18 (1H, m), 3.09 (1H, m), 3.20 (1H, dt, J=3.8, 12.4), 3.53 (1H, m), 3.67 (1H, m), 3.89 (1H, m), 4.07 (1H, s), 4.23 (1H, m), 4.39 (2H, m), 6.38 (1H, m), 6.49 (2H, m), 7.03 (2H, m), 7.46 (2H, m); MS (ES^+) m/z 389 (M+1, 100%).

Ex. No.	R^1	R^2	R^3	Data
64	2′-O-$(CH_2)_3$-3′		5′-F	^{1}H NMR (360MHz, DMSO) δ 1.71 (1H, m), 1.80 (1H, m), 2.18 (1H, m), 2.65 (2H, t, J=6.4), 3.27 (3H, m), 3.63 (1H, t, J=7.8), 3.73 (1H, m), 3.91 (3H, m), 4.17 (1H, m), 4.24 (1H, t, J=8), 4.73 (1H, s), 6.13 (1H, dd, J=9.6, 3), 6.69 (1H, dd, J=8.9, 3.1) 7.31 (2H, t, J=8.8), 7.67 (2H, m); MS (ES$^+$) m/z 388 (M+1, 100%).
65	2′-CH_2OH	H	H	^{1}H NMR (250MHz, $CDCl_3$) δ 1.72 (1H, dd, J=9.7, 12.8), 1.98 (2H, br s), 2.20 (1H, dd, J=8.1, 12.8), 2.41-2.45 (1H, m), 3.02 (1H, dd, J=2.1, 12.2), 3.18 (1H, ddd, J=3.6, 12.2, 12), 3.52-3.67 (3H, m), 3.82-3.97 (1H, m), 4.0 (1H, s), 4.20 (1H, ddd, J=3, 11.6, 11.6), 4.32 (1H, dd, J=8.2, 9.6), 6.47 (1H, dd, J=1.5, 7.3), 6.93-7.26 (5H, m), 7.50 (2H, dd, J=5.6, 8.6); MS (ES$^+$) m/z 344 (M+1, 100%).
66	2′-$OCH(CH_3)_2$	5-CF_3	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.24 (6H, dd, J=6.0, 10.3), 1.74 (1H, m), 2.21 (1H, m), 3.17 (2H, m), 3.65 (1H, m), 3.72 (1H, m), 3.94 (1H, m), 4.19 (1H, s), 4.40-4.55 (3H, m), 6.78 (2H, m), 6.99 (2H, m), 7.33 (1H, m), 7.61 (2H, m); MS (ES$^+$) m/z 439 (M+1, 100%).
67	2′-CH_3	5′-F	H	^{1}H NMR (360MHz, DMSO) δ 1.89 (3H, s), 1.90 (1H, m), 2.32 (1H, m), 2.55 (1H, m), 3.31 (2H, m), 3.83 (1H, t, J=8.5), 3.93 (1H, m), 4.11 (1H, t, J=7.7), 4.23 (1H, m), 4.70 (1H, s), 6.90 (1H, dt, J=8.4, J=2.8), 7.08 (2H, m), 7.36 (2H, t, J=8.9), 7.74 (2H, m); MS (ES$^+$) m/z 346 (M+1, 100%).
68	2′-OCH_2CHF_2	5′-F	H	^{1}H NMR (360MHz, DMSO) δ 1.64 (1H, m), 2.30 (1H, m), 3.28 (2H, m), 3.63 (1H, t, J=7.2), 3.83 (1H, t, J=7.6), 3.90 (1H, m), 4.21 (3H, m), 4.32 (1H, t, J=8.2), 4.76 (1H, s), 6.28 (1H, tt, J=54.5), 6.21 (1H, dd J=7.1), 6.95 (2H, m), 7.28 (2H, t, J=8.8), 7.67 (2H, m); MS (ES$^+$) m/z 412 (M+1, 100%).
69	2′-$OCH_2CH_2N(CH_3)_2$	5′-F	H	^{1}H NMR (360MHz, $CDCl_3$) δ 1.69 (1H, dd, J=12, 10), 2.15 (1H, dd, J=8, 12), 2.37 (6H, s), 2.74 (2H, t, J=8), 3.03 (1H, dd, J=2, 12), 3.17 (1H, dt, J=3.5, 12), 3.40 (2H, brs), 3.55 (1H, dd, J=6.8, 15), 3.65 (1H, dd, J=2, 12), 3.8-3.9 (3H, m), 4.18 (1H, dt, J=3.5, 12), 4.33 (1H, t, J=8), 6.15 (1H, dd, J=8.6, 2), 6.64-6.75 (2H, m), 6.96-7.06 (2H, m), 7.42-7.50 (2H, m); MS (ES$^+$) m/z 419 (M+1, 50%), 210 ($M^{+}/2$).
70	2′-OCH_2CH_2F	5′-F	H	^{1}H NMR (360MHz, DMSO) δ 1.66 (1H, m), 2.86 (1H, m), 3.15 (2H, m), 3.62 (1H, t, J=8.15), 3.84 (1H, t, J=8.4), 3.88 (1H, d, J=14.8), 4.10 (1H, m), 4.17 (2H, m), 4.32 (1H, t, J=8.3), 4.57 (1H, t, J=2.4), 4.70 (1H, t, J=2.5), 4.75 (1H, s), 6.23 (1H, dd, J=9.9, 2.5), 6.93 (2H, m), 7.28 (2H, t, J=8.89), 7.66 (2H, m); MS (ES$^+$) m/z 394 (M+1, 100%).

TABLE 2



Ex. No.	R^1	R^2	from Ex. No.	Data
71	OCH_3	H	10	^{1}H NMR (250MHz, $CDCl_3$) δ 1.84 (1H, m), 2.10 (1H, m), 2.21 (6H, s), 2.54 (1H, m), 2.84 (1H, d, J=11.3), 3.23 (1H, d, J=14), 3.76-3.48 (9H, m), 3.91 (1H, m), 4.20 (1H, m), 4.30 (1H, t, J=8), 6.57 (1H, dd, J=1.8, 8), 6.74 (2H, m), 7.14-7.02 (3H, m), 7.61 (2H, brs); MS (ES^+) m/z 482 (M+1, 100%).
72	OCF_3	H	37	^{1}H NMR (250MHz, $CDCl_3$) δ 1.68 (1H, m), 2.28 (7H, m), 2.57 (1H, m), 2.86 (1H, m), 3.30 (1H, d, J=14), 3.51-3.71 (6H, m), 3.93 (1H, m), 4.14 (1H, m), 4.30 (1H, t, J=8.4), 6.33 (1H, d, J=8.3), 6.95-7.10 (5H, m), 7.61 (2H, bs); MS (ES^+) m/z 535 (M+1, 100%).
73	$OCH(CH_3)_2$	5'-F	45	^{1}H NMR (250MHz, $CDCl_3$) δ 1.14 (1H, dd, J=6.1 and 8.6), 1.24 (6H, dd, J=2.8 and 6.0), 1.64 (1H, dd, J=9.8 and 9.8), 2.23 (1H, dd, J=7.9 and 12.7), 2.08 (6H, s), 3.56 (1H, dd, J=7.8 and 7.8), 3.68-3.80 (2H, m), 3.90-4.04 (3H, m), 4.20-4.45 (6H, m), 6.11 (1H, dd, J=2.8 and 9.6), 6.63-6.74 (2H, m), 7.11-7.20 (2H, m), 7.58-7.82 (2H, brm); MS (ES^+) m/z 527 (M+1, 100%).
74	OCH_3	5'-$CH(CH_3)_2$	47	^{1}H NMR (360MHz, $CDCl_3$) δ 1.10 (6H, d, J=6.9), 1.85 (1H, t, J=12.3), 2.09 (1H, m), 2.25 (6H, s), 2.54 (1H, dt, J=11.9, 3.5), 2.65 (1H, m), 2.84 (1H, m), 3.25 (1H, d, J=13.9), 3.54 (3H, m), 3.67 (1H, d, J=13.9), 3.90 (1H, m), 4.19 (1H, m), 4.29 (1H, t, J=8.3), 6.44 (1H, d, J=2.2), 6.66 (1H, d, J=8.4), 6.95 (1H, dd, J=8.3, 2.2), 7.07 (2H, t, J=8.7), 7.62 (2H, brs); MS (ES^+) m/z 524 (M+1, 100%).

Ex. No.	R^1	R^2	from Ex. No.	Data
75	OCH_2CH_3	5'-F	48	^{1}H NMR (360MHz, $CDCl_3$) δ 1.32 (3H, t, J=6.9), 1.72 (1H, m), 2.17 (1H, m), 2.30 (6H, s), 2.56 (1H, m), 2.81 (1H, m), 3.26 (1H, d, J=14.0), 3.48 (1H, m), 3.60 (5H, m), 3.89 (3H, m), 4.17 (1H, m), 4.33 (1H, m), 6.12 (1H, m), 6.64 (1H, m), 6.73 (1H, m), 7.04 (2H, m), 7.6 (2H, brs); MS (ES$^+$) m/z 514 (M+1, 100%).
76	$OCH_2CH_2CH_3$	H	44	^{1}H NMR (500MHz, $CDCl_3$) δ 1.00 (3H, t, J=7.4), 1.71 (3H, m), 2.14 (1H, m), 2.34 (6H, s), 2.80 (1H, d, J=10.4), 3.00 (1H, dt, J=11.9, 3.6), 3.13 (1H, d, J=17.3), 3.25 (1H, d, J=17.3), 3.31 (2H, s), 3.52 (1H, t, J=8.1), 3.71 (1H, s), 3.73 (1H, d, J=2.91), 3.82 (2H, t, J=6.5), 3.96 (1H, m), 4.34 (2H, m), 6.46 (1H, d, J=6.4), 6.70 (2H, m), 7.00 (2H, t, J=8.6), 7.06 (1H, m), 7.51 (1H, brs).
77	OCH_3	5'-CF_3	62	^{1}H NMR (360MHz, $CDCl_3$) δ 1.82 (1H, t, J=10), 2.14 (1H, dd, J=8, 12), 2.19 (6H, s), 2.55 (1H, td, J=3.6,12), 2.85 (1H, brd), 3.22 (1H, d, J=14), 3.46 (2H, s), 3.54 (1H, t, J=8), 3.57 (1H, s), 3.63 (1H, brd), 3.68 (3H, s), 3.90 (1H, mc), 4.18 (1H, brt), 4.29 (1H, t, J=8), 6.77 (1H, d, J=8.5), 6.82 (1H, d, J=2), 7.05 (2H, t, J=8.5), 7.36 (1H, dd, J=2, 8.5), 7.60 (2H, m); MS (ES$^+$) m/z 550 (M+1, 100%).
78	$OCH(CH_3)_2$	4'-F	63	^{1}H NMR (360MHz, $CDCl_3$) δ 1.24 (6H, m), 1.71 (1H, m), 2.11 (1H, m), 2.20 (6H, s), 2.54 (1H, dt, J=3.4, 11.9), 2.83 (1H, d, J=11.5), 2.97 (1H, d, J=11.9), 3.21 (1H, d, J=13.9), 3.44 (3H, m), 3.56 (1H, s), 3.67 (2H, m), 3.87 (1H, m), 4.22 (1H, m), 4.30-4.43 (2H, m), 6.36 (2H, m), 6.45 (1H, d, J=11.0), 7.04 (2H, m), 7.59 (2H, vbs); MS (ES$^+$) m/z 527 (M+1, 100%).

EXAMPLE 79

(2S,3S,9S)-4-Aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl)spiro[5.4]decane

The title compound was obtained from the compound of Example 33 according to the method of Example 7.

^{1}H NMR (250MHz, $CDCl_3$) δ 1.75 (1H, m), 2.33 (1H, m), 2.56 (1H, m), 2.95 (2H, m), 3.46-3.68 (5H, m), 4.14 (1H, m), 4.40 (1H, m), 6.80 (1H, d, J=7.7), 6.96 (1H, s), 7.07 (2H, d, J=8.3), 7.26 (1H, m), 7.38 (1H, d), 7.58 (2H, vbs), 10.37 (1H, s), 10.90 (1H, s).

EXAMPLE 80

(2S,3S,9S)-4-Aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)-spiro[5.4]decane

The title compound was obtained from the compound of Description 14 and 2-naphthalene boronic acid according to the method of Example 9.

^{1}H NMR (250MHz, $CDCl_3$) δ 2.01 (1H, dd, J=12.8, 3.0), 2.29 (1H, dd, J=12.8, 8.0), 3.07 (1H, dd, J=12.2, 2.4), 3.21 (1H, dt, J=12.2,3.5), 3.71 (1H, dd, J=11.3, 3.0), 3.84 (1H, t, J=7.6), 3.93 (1H, s), 4.07 (1H, s), 4.27-4.41 (2H, m), 4.47 (1H, t, J=8.3), 6.85 (1H, d, J=7.0), 7.00 (2H, t, J=8.7), 7.20 (1H, t, J=7.7), 7.31-7.51 (4H, m), 7.62 (1H, d, J=8.2), 7.74-7.79 (2H, m); MS (ES^+) m/z 364 (M+1, 100%).

EXAMPLE 81

(2S,3S,9S)-4-Aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)spiro[5.4]decane

The title compound was obtained from the compound of Example 80 according to the method of Example 7.

^{1}H NMR (360MHz, d_6-DMSO) δ 1.90 (1H, dd, J=12.9, 9.3), 2.30 (1H, dd, J=12.8, 8.4), 2.45 (1H, m), 2.80 (1H, dd, J=14.0, 7.7), 3.27 (1H, d, J=14.0), 3.58-3.69 (3H, m), 4.07-4.21 (2H, m), 4.31 (1H, t, J=8.3), 6.76 (1H, d, J=7.0), 7.13 (2H, t, J=8.8), 7.20 (1H, t, J=7.7), 7.30 (1H, t, J=7.7), 7.45

(1H, t, J=7.5), 7.59-7.70 (4H, m), 7.85 (1H, d, J=8.0), 11.22 (1H, s), 11.26 (1H, bs); MS (ES^+) m/z 461 (M+1, 100%).

EXAMPLE 82

(2S,3S,9S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-thiomethylphenyl)spiro[5.4]decane

a) (2S,3S,9S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-thiomethylphenyl)spiro[5.4]dec-9-ene

The title compound was obtained from the compound of Description 14 and 2-thiomethylphenylboronic acid according to the method of Example 9, step (a).

^1H NMR (360MHz, $CDCl_3$) δ 2.31 (3H, s), 2.38 (1H, dt, J=12.1, 3.6), 2.83 (2H, d, J=13.4), 3.62 (1H, s), 3.76 (2H, m), 4.33 (2H, m), 4.90 (1H, dd, J=13.1, 2.2), 5.91 (1H, s), 6.80 (1H, dd, J=7.7, 1.4), 6.96-7.05 (3H, m), 7.13-7.30 (7H, m), 7.58 (2H, br); MS (ES^+) m/z 448 (M+1, 100%).

b) (2S,3S,9S)-4-Aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-thiomethylphenyl)spiro[5.4]decane

The compound of step (a) (266mg, 0.59mmol) in benzene:ethanol (1:1, 10ml) was hydrogenated under one atmosphere of hydrogen for 18 hours with Wilkinson's catalyst (50mg). The reaction mixture was filtered through hyflo™, concentrated to a crude oil (361mg) and purified by flash silica gel chromatography eluting with 6:1 hexane:ethyl acetate to yield the title compound as an oil (236mg, 88%).

^1H NMR (360MHz, $CDCl_3$) δ 1.71 (1H, dd, J=12.9, 9.0), 2.13-2.27 (2H, m), 2.27 (3H, s), 2.67-2.76 (2H, m), 3.37 (1H, s), 3.41-3.52 (2H, m), 3.62 (1H, d, J=13.2), 3.97 (1H, m), 4.09 (1H, dt, J=11.6, 2.2), 4.23 (1H, t, J=8.2), 6.20 (1H, dd, J=7.6, 1.0), 6.77 (1H, dt, J=7.0, 0.7), 6.88-7.18 (9H, m), 7.52 (2H, bs); MS (ES^+) m/z 450 (M+1, 100%).

EXAMPLE 83

(2S,3S,9S)-4-Aza-1,7-dioxa-9-(5-fluoro-2-methoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane

a) (2S,3S,9S)-4-Aza-1,7-dioxa-9-(5-fluoro-2-methoxyphenyl)-3-(4-fluorophenyl)-4-(N-*p*-toluenesulfonyl-1,3-imidazol-4-ylmethyl)-spiro[5.4]decane

The product of Example 41 (55mg, 0.14mmol) was dissolved in N,N-dimethylformamide (1ml) and potassium carbonate added (58mg, 0.42mmol), followed by the product of Description 29 (69mg, 0.21mmol). The reaction mixture was stirred at room temperature for 12 hours, then diluted with water (10ml) and extracted with ethyl acetate (3x30ml). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification on flash silica, eluting with 5% methanol/dichloromethane gave the title compound. M/S ES^+=596 100%.

b) (2S,3S,9S)-4-Aza-1,7-dioxa-9-(5-fluoro-2-methoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane

The product of step (a) was dissolved in methanol/HCl (15ml) and stirred at room temperature for 2½ hours. The reaction was concentrated *in vacuo*, and the residue triturated with ether (x5) to yield the title compound as a pale yellow solid (45mg). ^1H NMR (360MHz, d_6-DMSO) δ 1.70 (1H, t, J=9.7), 2.16 (1H, t, J=12.8), 3.50 (2H, m), 3.72 (5H, m), 4.15 (2H, t, J=8.3), 6.18 (1H, m), 6.86 (2H, m), 7.11 (1H, d, J=7.75), 7.23 (2H, m), 7.46 (2H, d, J=8), 7.73 (2H, brs), 9.05 (1H, s). MS ES^+=442 100%.

Similarly prepared was:

EXAMPLE 84

(2S,3S,9S)-4-Aza-1,7-dioxa-9-(5-fluoro-2-isopropoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane

From the product of Example 45 and the product of Description 29. MS (ES^+) m/z 470 (M+1, 100%).

EXAMPLE 85

(2S,3S,9S)-4-Aza-4-benzyl-9-(2,5-dimethoxyphenyl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane

The product of Example 42 (200mg), benzyl bromide (70µl) and potassium carbonate (220mg) were suspended in dimethylformamide (2ml) and the mixture was heated to 60°C for 2 hours. The mixture was cooled and diluted with water (30ml) and ethyl acetate (20ml). The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica using 10-20% ethyl acetate in hexane as eluant to give the title compound as a white solid.

^1H NMR (250MHz, d_6-DMSO) δ 1.88 (1H, t, J=10), 2.18 (1H, dd, J=8, 12.5), 2.32-2.41 (1H, m), 2.74-2.79 (1H, m), 2.93 (1H, d, J=12.5), 3.34 (1H, t, J=8), 3.61-3.68 (3H, m), 3.68 (3H, s), 3.69 (3H, s), 3.80-3.91 (1H, m), 4.08-4.17 (1H, m), 4.24 (1H, t, J=8), 6.16 (1H, d, J=3), 6.78 (1H, dd, J=3, 9), 6.90 (1H, d, J=9), 7.28-7.45 (7H, m), 7.77-7.83 (2H, m); MS (ES^+) m/z 464 (M+1, 100%).

EXAMPLE 86

(2S,3S,9S)-4-Aza-4-(carbonylmethylpyrrolidin-1-yl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane

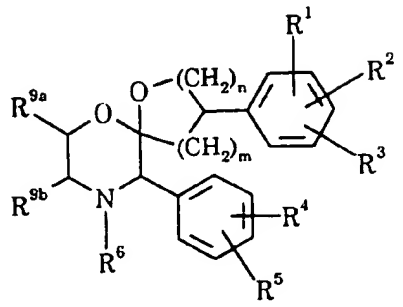
To a solution of the product of Example 10 (160mg, 0.47mmol), pyrrolidine acetic acid (92mg, 0.56mmol), and triethylamine (78µl, 0.56mmol) in dry dimethylformamide (3ml) was added hydroxy benzotriazole trihydrate (HOBT; 65mg, 0.49mmol) then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCDI; 91mg, 0.49mmol). The reaction mixture was stirred at room temperature for 72 hours, diluted with water, then extracted with ethyl acetate (3x). The

combined organic extracts were washed with brine (1x) then dried ($MgSO_4$) and concentrated to leave a brown oil. Purification on silica gel eluting with dichloromethane/methanol/ammonia (95:5:0.25 then 90:10:0.25) provided the title compound as a pale-yellow foam.

^1H NMR (250MHz, $CDCl_3$) δ 1.78 (4H, brs), 2.22 (1H, m), 2.60 (5H, m), 3.47-3.32 (3H, m), 4.07-3.74 (8H, m), 4.43 (1H, t, J=8), 5.56 (1H, brs), 6.85 (2H, m), 7.01 (3H, m), 7.20 (1H, m), 7.61 (2H, m); MS (ES^+) m/z 455 (M+1, 100%).

CLAIMS:

1. A compound of the formula (I):



(I)

wherein

R^1 represents hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, C_{1-4}alkyl substituted by a C_{1-4}alkoxy or hydroxy group, hydroxy, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, NR^aR^b, $SO_2NR^aR^b$, or OC_{1-4}alkylNR^aR^b, where R^a and R^b are each independently hydrogen or C_{1-4}alkyl;

R^2 and R^3 each independently represent hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or trifluoromethyl;

or, where R^1 and $R^2$are attached to adjacent carbon atoms, they may be joined such that, together with the carbon atoms to which they are attached, there is formed a 5- or 6-membered ring optionally containing 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen, or 1 or 2 groups selected from S(O), $S(O)_2$ and NR^a, which ring may also contain 1 or 2 double bonds, where R^a is as previously defined;

R^4 represents hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, C_{1-4}alkyl substituted by a C_{1-4}alkoxy group, trifluoromethyl, nitro, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$ where R^a and R^b are as previously defined;

R^5 represents hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or trifluoromethyl;

R^6 represents hydrogen, COR^a, CO_2R^a, $COCONR^aR^b$, $COCO_2R^a$, C_{1-6}alkyl optionally substituted by a group selected from (CO_2R^a, $CONR^aR^b$, hydroxy, CN, COR^a, NR^aR^b, $C(NOH)NR^aR^b$, $CONHphenyl(C_{1-4}alkyl)$, $COCO_2R^a$, $CONHNR^aR^b$, $C(S)NR^aR^b$, $CONR^aC_{1-6}alkylR^{12}$, $CONR^{13}C_{2-6}$alkenyl, $CONR^{13}C_{2-6}$alkynyl, $COCONR^aR^b$, $CONR^aC(NR^b)NR^aR^b$, $CONR^a$heteroaryl, and phenyl optionally substituted by one, two or three substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen and trifluoromethyl) or C_{1-6}alkyl, optionally substituted by oxo, substituted by a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkyl;

R^7 is hydrogen or C_{1-4}alkyl, C_{3-7}cycloalkyl, $C_{3-7}cycloalkylC_{1-4}$alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen or C_{1-4}alkyl, C_{3-7}cycloalkyl, $C_{3-7}cycloalkylC_{1-4}$alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkoxy optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} each independently represent hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

R^{12} represents OR^a, $CONR^aR^b$ or heteroaryl;

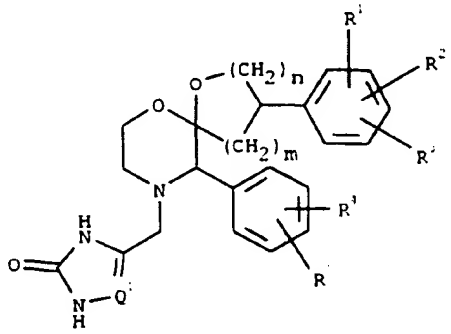
R^{13} represents H or C_{1-6}alkyl;

m is zero, 1, 2 or 3; and

n is zero, 1, 2 or 3; with the proviso that the sum total of m and n is 2 or 3;

or a pharmaceutically acceptable salt thereof.

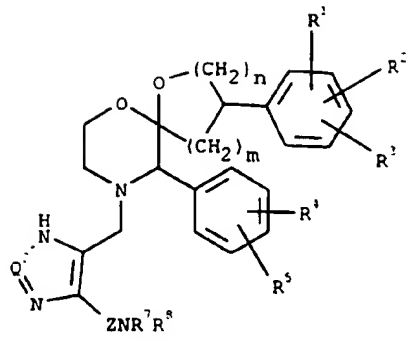
2. A compound as claimed in claim 1 of the formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein R^1, R^2, R^3, R^4, R^5, m and n are as defined in claim 1 and Q^1 is CH, N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in claim 1.

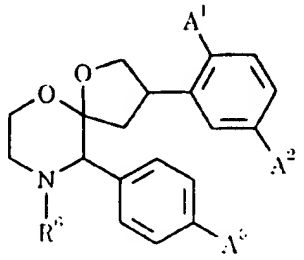
3. A compound as claimed in claim 1 of the formula (Ib) or a pharmaceutically acceptable salt thereof:



(Ib)

wherein R^1, R^2, R^3, R^4, R^5, m and n are defined in claim 1, Q^2 is CH or N and Z. R^7 and R^8 are as defined in claim 1.

4. A compound as claimed in claim 1 of the formula (Ic) or a pharmaceutically acceptable salt thereof:



(Ic)

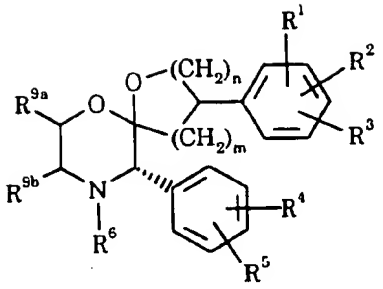
wherein R^6 is as defined in claim 1;

A^1 is C_{1-4}alkoxy;

A^2 is hydrogen, halogen, C_{1-4}alkyl or fluoroC_{1-4}alkyl; and

A^3 is hydrogen or halogen.

5. A compound as claimed in claim 1 of the formula (Id) or a pharmaceutically acceptable salt thereof



(Id)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b}, m and n are as defined in claim 1.

6. A compound as claimed in any one of claims 1 to 3 wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

7. A compound as claimed in any one of claims 1 to 3 wherein R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

8. A compound as claimed in any one of claims 1 to 3 wherein R^3 is hydrogen, fluorine, chlorine or CF_3.

9. A compound as claimed in any one of claims 1 to 3 wherein R^4 is hydrogen.

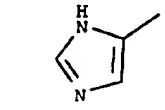
10. A compound as claimed in any one of claims 1 to 3 wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

11. A compound as claimed in any one of claims 1 to 3 wherein n is 1.

12. A compound as claimed in any one of claims 1 to 3 wherein m is 1 or 2.

13. A compound as claimed in any one of claims 1 to 12 wherein R^6 is C_{1-6}alkyl substituted by a 5-membered heterocyclic ring containing 2 or 3 nitrogen atoms, which ring is optionally substituted by =O or =S and which ring is optionally substituted by a group of the formula ZNR^7R^8 where Z, R^7 and R^8 are as defined in claim 1.

14. A compound as claimed in claim 13 wherein the heterocyclic ring is selected from: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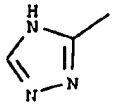
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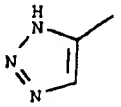
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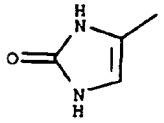
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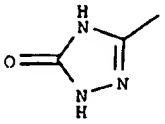
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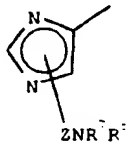
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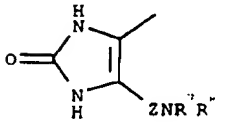
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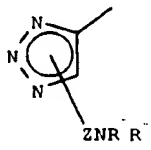
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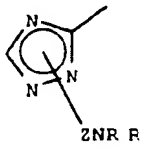
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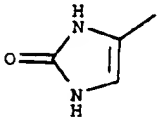
15. A compound as claimed in claim 14 wherein the heterocyclic ring is selected from: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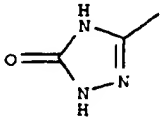
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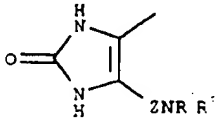
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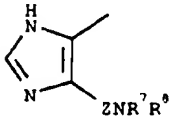
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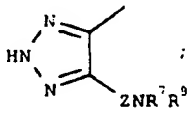
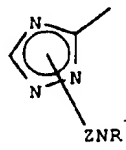

; and

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16. A compound as claimed in any one of claims 1 to 15 wherein Z is CH_2.

17. A compound as claimed in any one of claims 1 to 16 wherein R^7 is a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, R^8 is a C_{1-4}alkyl group or a C_{1-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, or R^7 and R^8 are linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxy or C_{1-2}alkoxy group.

18. A compound as claimed in any one of claims 1 to 17 wherein Z is CH_2 and NR^7R^8 is dimethylamino, azetidinyl or pyrrolidino.

19. A compound selected from:
(2S,3S,9R)-4-aza-1,7-dioxa-3,9-diphenylspiro[5.5]undecane;
(2S,3S,9S)-4-aza-1,7-dioxa-3,9-diphenyl-spiro[5,5]undecane;
(2R,3S,9S)-4-aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane;
(2R,3S,9R)-4-aza-4-benzyl-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane;
(2S,3S,9S)-4-aza-1,7-dioxa-3,9-diphenyl-spiro[5.5]undecane-4-ylmethyl)-2,4-dihydro-1,2,4-triazol-3-one;
4-aza-4-benzyl-1,7-dioxa-3,8-diphenyl-spiro[5.4]decane;
or a pharmaceutically acceptable salt thereof.

20. A compound selected from:
(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-phenylspiro[5.4]decane;
(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-methoxyphenyl) spiro[5.4]decane;

(2R,3S,8R)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

(2R,3S,8S)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

(2R,3S,8R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

(2R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

(2R,3S,8R)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

(2R,3S,8S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-8-phenyl-spiro[5.4]decane;

4-aza-4-benzyl-7-dioxa-5-phenyl-9-(2-trifluoromethyl-phenyl)-spiro[5.5]undecane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethylphenyl) spiro[5.5]undecane;

(3R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-trifluoromethylphenyl) spiro[5.5]undecane;

(2R,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethyl)phenyl) spiro[5.5]undecane;

4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl) spiro[5.5]undecane;

(2R,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2R,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9R)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl) phenyl)spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-benzyl-7-dioxa-5-phenyl-9-(2-(trifluoromethoxy) phenyl)-spiro[5.5]undecane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy) phenyl)spiro[5.5]undecane;

4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-(trifluoromethoxy)phenyl) spiro[5.5]undecane;

(2S,3S,9S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(3-(trifluoromethyl)phenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)-spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-naphthyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-benzyl-1,7-dioxa-3-(4-fluorophenyl)-9-(2-thiomethylphenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-1,7-dioxa-9-(5-fluoro-2-methoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane;

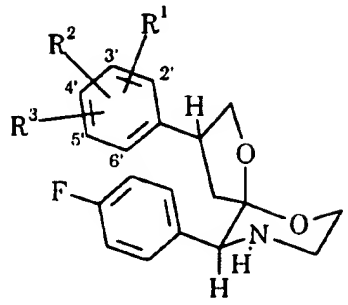
(2S,3S,9S)-4-aza-1,7-dioxa-9-(5-fluoro-2-isopropoxyphenyl)-3-(4-fluorophenyl)-4-(1,3-imidazol-4-ylmethyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-benzyl-9-(2,5-dimethoxyphenyl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane;

(2S,3S,9S)-4-aza-4-(carbonylmethylpyrrolidin-1-yl)-1,7-dioxa-3-(4-fluorophenyl)spiro[5.4]decane;

or a pharmaceutically acceptable salt thereof.

21. A compound of the formula



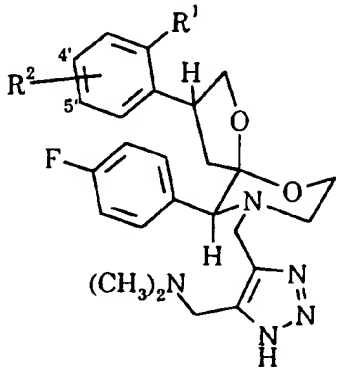
selected from the compounds in which R^1, R^2 and R^3 take the following definitions:

Ex. No.	R^1	R^2	R^3
33	3'-CF_3	H	H
34	2'-CF_3	H	H
35	4'-OCH_3	H	H
36	2'-CH_3	H	H
37	2'-OCF_3	H	H
38	3'-OCH_3	H	H
39	3'-NH_2	H	H
40	3'-$OCH(CH_3)_2$	H	H
41	2'-OCH_3	5'-F	H
42	2'-OCH_3	5'-OCH_3	H
43	2'-$OCH(CH_3)_2$	H	H
44	2'-$O(CH_2)_2CH_3$	H	H
45	2'-$OCH(CH_3)_2$	5'-F	H
46	2'-$OCH(CH_3)_2$	5'-$CH(CH_3)_2$	H
47	2'-OCH_3	5'-$CH(CH_3)_2$	H
48	2'-OCH_2CH_3	5'-F	H
49	2'-OCH_3	5'-$C(CH_3)_3$	H
50	2'-OH	H	H

Ex. No.	R^1	R^2	R^3
51	2′-OCH_2CH_2-3′		H
52	2′-OCH_3	6′-F	H
53	2′-CH_3	3′-F	H
54	3′-CH_3	5′-CH_3	H
55	2′-OCH_3	3′-OCH_3	H
56	2′-$C(O)N(CH_2CH_3)_2$	H	H
57	2′-$OCH(CH_3)_2$	4′-F	5′-F
58	2′-$S(O)_2N(CH_2CH_3)_2$	H	H
59	2′-$NH-(CH_2)_3$-3′		H
60	2′-F	5′-F	H
61	2′-O-CH_2-O-3′		H
62	2′-OCH_3	5′-CF_3	H
63	2′-$OCH(CH_3)_2$	4′-F	H
64	2′-O-$(CH_2)_3$-3′		5′-F
65	2′-CH_2OH	H	H
66	2′-$OCH(CH_3)_2$	5-CF_3	H
67	2′-CH_3	5′-F	H
68	2′-OCH_2CHF_2	5′-F	H
69	2′-$OCH_2CH_2N(CH_3)_2$	5′-F	H
70	2′-OCH_2CH_2F	5′-F	H

or a pharmaceutically acceptable salt thereof.

22. A compound of the formula



selected from the compounds in which R^1 and R^2 take the following definitions:

Ex. No.	R^1	R^2
71	OCH_3	H
72	OCF_3	H
73	$OCH(CH_3)_2$	5'-F
74	OCH_3	5'-$CH(CH_3)_2$
75	OCH_2CH_3	5'-F
76	$OCH_2CH_2CH_3$	H
77	OCH_3	5'-CF_3
78	$OCH(CH_3)_2$	4'-F

or a pharmaceutically acceptable salt thereof.

23. A compound as claimed in any preceding claim for use in therapy.

24. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 22 in association with a pharmaceutically acceptable carrier or excipient.

25. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

26. A method according to claim 25 for the treatment or prevention of pain or inflammation.

27. A method according to claim 25 for the treatment or prevention of migraine.

28. A method according to claim 25 for the treatment or prevention of emesis.

29. A method according to claim 25 for the treatment or prevention of postherpetic neuralgia.

30. The use of a compound as claimed in any one of claims 1 to 22 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

31. The use of a compound as claimed in any one of claims 1 to 22 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

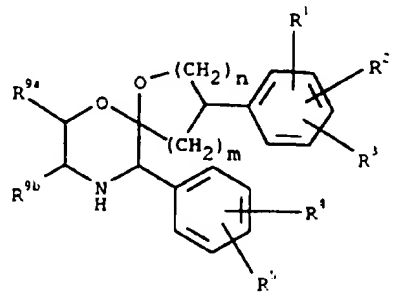
32. The use of a compound as claimed in any one of claims 1 to 22 for the manufacture of a medicament for the treatment or prevention of migraine.

33. The use of a compound as claimed in any one of claims 1 to 22 for the manufacture of a medicament for the treatment or prevention of emesis.

34. The use of a compound as claimed in any one of claims 1 to 22 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.

35. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A), for a compound of formula (I) in which R^6 is other than H, reaction of a compound of formula (II)



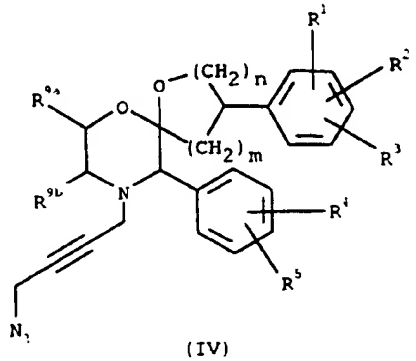
(II)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, m and n are as defined in claim 1 with a compound of formula (III):

$$LG\text{-}R^{6a} \qquad (III)$$

where R^{6a} is a group of the formula R^6 as defined in claim 1 or a precursor therefor and LG is a leaving group; and, if R^{6a} is a precursor group, converting it to a group R^6; or

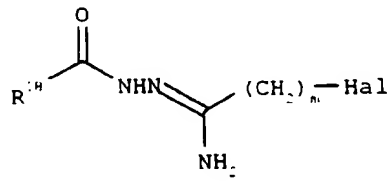
(B), for a compound of formula (I) wherein R^6 represents a 1,2,3-triazol-4-ylmethyl group substituted by $CH_2NR^7R^8$, reaction of a compound of formula (IV)



(IV)

with an amine of formula NHR^7R^8; or

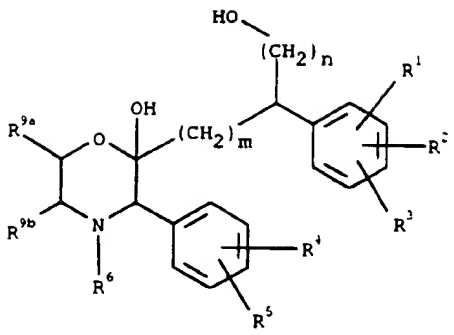
(C), for a compound of formula (I) wherein R^6 represents a C_{1-6}alkyl group which is substituted by an unsubstituted or substituted 1,2,4-triazolyl group, reaction of an intermediate of formula (II) with a compound of formula (V)



(V)

wherein Hal is a halogen atom, m is an integer from 1 to 6 and R^{18} is H, $CONH_2$ or OCH_3, followed where necessary by conversion to a compound of formula (I); or

(D), from a compound of formula (VI)

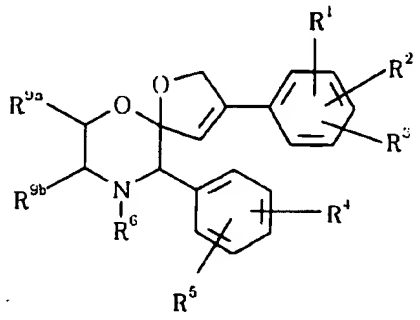


(VI)

by an acid catalysed intramolecular cyclisation reaction; or

(E), by interconversion from another compound of formula (I); or

(F) for a compound of formula (I) in which n is 1 and m is 1, reduction of a compound of formula (XX)



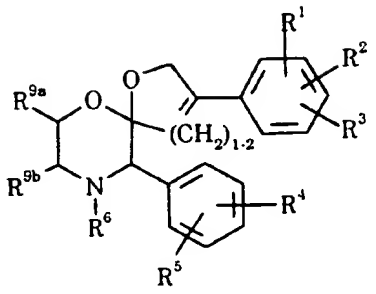
(XX)

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt thereof.

36. A compound of the formula (XX)



(XX)

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^{9a} and R^{9b} are as defined in claim 1;

or a salt thereof.

INTERNATIONAL SEARCH REPORT

Intern d Application No
PCT/GB 95/02927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/10 A61K31/535 //(C07D498/10,307:00,265:00), (C07D498/10,311:00,265:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 577 394 (MERCK) 5 January 1994 cited in the application see claims 1,6,7 ---	1,21, 31-34
A	TETRAHEDRON LETTERS, vol. 22, no. 15, 1981 pages 1403-1406, C. AMSTERDAMSKY ET AL 'Une nouvelle méthoxylation d'hydroperoxy-3-indolines issues de la photo-oxygénation d'indoles en milieu réducteur' see page 1403; example 3 --- -/--	1,21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1996	01.03.1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. d Application No
PCT/GB 95/02927

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF ORGANIC CHEMISTRY, vol. 25, 1960 pages 928-931, R. E. LUTZ ET AL 'Acid-base effects in the ring-chain tautomerism of alpha-((beta-hydroxyethyl)-amino)desoxybenzoins' see page 928, left column -----	1,21

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ..ational application No.
PCT/GB95/02927

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-29 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/GB 95/02927

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-577394	05-01-94	AU-B-	4156893	06-01-94
		AU-B-	4656193	24-01-94
		CA-A-	2099233	30-12-93
		CN-A-	1087902	15-06-94
		CZ-A-	9403330	13-09-95
		FI-A-	946133	28-12-94
		HR-A-	931003	28-02-95
		JP-A-	6172178	21-06-94
		NO-A-	945064	28-02-95
		SI-A-	9300346	31-12-93
		SK-A-	160094	11-07-95
		WO-A-	9400440	06-01-94
		AU-B-	4160893	06-01-94
		ZA-A-	9304624	20-06-94